AGING AND MENTAL HEALTH

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AGING AND MENTAL HEALTH

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People are progressively ageing all over the world, and it is estimated that the number of persons aged 60 or over will more than triple by 2100. This emerging population will experience an inevitable rise in dementia, mental health problems and chronic diseases.

According to GBD (2010), neuropsychiatric disorders among older adults account for 6.6% of the total disability (DALYs) for this age group, with 15% suffering from a mental disorder.

Multiple social, psychological and biological factors are determinant of mental health, as well as life stressors. Among these, the lack of independence, limited mobility, chronic diseases, pain, frailty or other mental and physical problems require long-term care.

Beyond this, the elderly are more prone to experience events such as bereavement, a drop in socio-economic status, disability, which leads to isolation, loss of independence, loneliness and psychological distress.

Mental health problems and needs assessment by health-care professionals and older people themselves are under-recognised, and the stigma surrounding mental illness makes people reluctant to seek help.

The early investigation and diagnosis of these situations are crucial, as well as prior management with an important combination of pharmacological and psychosocial interventions, in conjunction with caregivers' and families' support.

The present book aims to contribute to the development of knowledge in Aging and Mental Health, taking different approaches from authors, coming from diverse scientific fields, with the final goal being the improvement of quality of life and healthy aging for this growing population.

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Table of Contents

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EDITORIAL
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Editorial: Aging and Mental Health

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Editorial on the Research Topic

Aging and Mental Health

According to the "Mental Health Action Plan 2013–2020" (WHO, 2013), mental health is an integral part of health and well-being and includes not only individual characteristics but also social, cultural, economic political, and environmental factors. The report recognizes that depending on the context certain groups, such as older people, are at higher risk of having mental health problems and consequently having higher rates of disability and mortality.

The main issues concerning aging and mental health are prevention, early diagnosis, recognition of major diseases, treatment and quality of life interventions, at both individual and community level.

Available knowledge about the aging process and mental health is still insufficient and the challenges of aging populations claim more research efforts into clinical conditions, older people's needs, and pathways of care. With the increase in average life expectancy, chronic conditions inherent to aging, such as dementias (in particular Alzheimer's Disease), are inevitably growing along with related behavioral and psychological disorders, which highlights the need for specific interventions in elderly mental health problems. Beside dementia and mild cognitive impairment, other issues like frailty, delirium and the risk for mental health problems or the unmet needs of older people, require substantially more attention from professionals and policy agents. The burden of mental health problems is frequently considered as an inevitable part of the process of aging, worsening the already negative stereotype about being old. Mental health issues, particularly those affecting old age are frequently underestimated, adding to the suffering of a large number of people who could be treated and benefit from diverse social and health care interventions to enhance their well-being. The comprehension of mechanisms underlying diseases, on a time diagnosis, and customized interventions will be much more cost-effective than just allowing the disease to progress, leading to the institutionalization of individuals, which has proved to be an adverse and expensive outcome, both for individuals and the community.

Taking this into consideration, the present Research Topic on "Aging and Mental Health" by Frontiers in Aging Neuroscience makes a contribution with updates and different perspectives on this important theme, developed over 17 papers. These updates focus on cognitive functions, neural and cellular mechanisms, delirium and mild cognitive impairment as well as the effects of exercise and health care settings.

The authors Lim and Yu have conducted an interesting review on the relation between aging and wisdom: age-related changes in economic and social decision making. They discuss this topic based on a model proposing five subcomponents of wisdom: (1) prosocial behavior in experimental economic games and competitive situations; (2) resolving social conflicts; (3) emotional homeostasis; (4) self-reflection; (5) dealing effectively with uncertainty in the domains

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of risk, ambiguity and intertemporal choice. They highlight that older adults outperform young adults in certain subcomponents of wisdom, but the exact relationship between old age and each subcomponent remains unclear.

Alves et al. addresses an interesting topic, based on the diversion paradigm developed by Delaney et al. (2010). The authors aim to determine whether thinking about an autobiographical memory interferes with the recall of recently encoded information, and to explore the degree of forgetfulness depending on the temporal distance from the diversionary thought. They conclude that the expected amnesic effect of diversionary thought was reached, but the temporal distance (old event vs. recent event) did not influence the recall of previously encoded information.

Szatloczki et al. point out the role of linguistic screening for early detection of Alzheimer's disease. The authors have produced a comprehensive review, concluding that AD can be more sensitively detected with the help of linguistic analysis than with other cognitive examinations, which would have relevant clinical implications.

The paper by Meng et al. examines the impact of aging on the brain's susceptibility to affective pictures of varying emotional intensities, with results that suggest that older adults are more resistant to the impact of negative stimuli, while they are equipped with enhanced attentional bias for positive stimuli.

Two studies about delirium are presented in this Research Topic. The first one by Androsova et al. is an interesting, clinically relevant literature review focused on the "Biomarkers of postoperative delirium and cognitive dysfunction". Bearing in mind that the pathogenesis of these postoperative cognitive impairments is multifactorial, the authors emphasize that the application of integrated systems biology has the potential to reconstruct the underlying network of molecular mechanisms and help in the identification of prognostic and diagnostic biomarkers. The second one, produced by Shi et al., finds a good reliability of MDAS and the cutoff point for diagnosis of delirium.

Coelho et al. have written an article about "Determinants of frailty: the added value of assessing medication". With this they analyse in general the determinants that predict frailty, as well as each frailty domain (physical, psychological, and social), considering the integral conceptual model of frailty. Particularly, the contribution of different daily-consumed medication is analyzed. The results add important information about which factors may precipitate states of high vulnerability in community dwelling elderly.

The article "Mismatch negativity (MMN) latency as a biomarker of amnestic mild cognitive impairment in Chinese rural elders" by Ji et al., aims to assess the mismatch negativity (MMN) component, a correlate of the automatic detection of changes in the acoustic environment, in healthy adults, and adults with amnestic mild cognitive impairment (aMCI). They find that while no difference was observed in amplitude between the two groups, there was a significant increase in the latency of the MMN in the aMCI group, which could be a sensitive, specific biomarker.

Akintola et al. have written a broad systematic review and meta-analysis concerning "Subclinical hypothyroidism (SCH) and cognitive function in people over 60 years". This meta-analysis, performed to assess available evidence on the association of SCH with cognition in community dwelling, relatively healthy older adults, found no evidence concerning this association.

Bearing in mind the well-known importance of regular exercise in benefiting mental and physical health in the elderly Santa Mina et al. have written the article "The acute effects of exercise on cortical excitation and psychosocial outcomes in men treated for prostate cancer: a randomized controlled trial". They have evaluated and presented novel findings of the effect of a single bout of exercise (low-moderate intensity) on psychological well-being and cortical silent period in prostate cancer survivors.

Paúl et al. have conducted a cross-sectional study about "Perceived risk of mental health problems in primary care" using the Portuguese version of RISC as a useful tool for early identification of mental health concerns in older patients. This study emphasizes the importance of healthcare professionals identifying patients at high risk of adverse outcomes early on in order to direct an appropriate intervention.

Bearing in mind that unmet needs are becoming acknowledged as better predictors of the worst prognostic outcomes than common measures of functional or cognitive decline, the article "Needs in nursing homes and their relation with cognitive and functional decline, behavioral and psychological symptoms" by Ferreira et al. will be a valuable aid to all those interested in learning about this issue. The authors have found more unmet needs associated with the worst outcomes, demonstrating that the needs of those institutionalized elderly remain under-diagnosed and untreated.

In the same setting of the nursing home, Caravau and Martin have written the paper "Direct costs of dementia in nursing homes". The authors deal with an interesting and poorly-studied topic, concluding that direct costs of dementia patients in Portugal exceed the costs of similar non-demented patients by a significant degree, which is in agreement with previous European studies, with direct implications for the provision of services for the management of the increasing prevalence of dementia.

The manuscript by Bastos et al. analyses "The importance of neighborhood ecological assets in community-dwelling old people's aging outcomes: A study in Northern Portugal," concludes that cognitive performance decreases in persons with the worst outdoor mobility, and also that depressive symptoms are less common with a greater number of recreation opportunities, suggesting that aging policies and practices must be ecologically embedded.

Finally, two commentaries have been written, the first of which also has a response. Craig has written a commentary on "Mental distress in patients with cerebral visual injury assessed with the German Brief Symptom Inventory" by Gall et al.. The second commentary written by Heine is about the article "Mental health and dual sensory loss (DSL) in older adults: a systematic review", by Heine and Browning (2014). This text focuses on the lack of solid data on the present subject, and also the need to diagnose and manage DSL early and effectively.

We hope that this Frontiers Research Topic will be an enrichment for Ageing and Mental Health issues, with the

efforts and commitments of all authors to whom we give our acknowledgement, as well as to the reviewers who have contributed by improving and clarifying these diverse contributions.

Finally, a special thanks for the support for publishing by the sponsor Pfizer, for three articles (Paúl et al.; Caravau and Martin; Bastos et al.). The sponsor did not play any role in the design, methods, data collection and analyses, or in the preparation of these articles.

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LF and CP have written this editorial for the Research Topic they have edited.

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REVIEW
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Aging and wisdom: age-related changes in economic and social decision making

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World life expectancy is increasing and many populations will begin to age rapidly. The impeding prevalence of a greater number of older people living longer lives will have significant social and economic implications. It is important to understand how older people make economic and social decisions. Aging can be associated with a "phenomenon of decline" and also greater wisdom. This paper seeks to examine the relationship between wisdom and aging. It reviews and connects the behavioral sciences and neuroscience literature on age differences in the following social and economic decision making domains that represent subcomponents of wisdom: (1) prosocial behavior in experimental economic games and competitive situations; (2) resolving social conflicts; (3) emotional homeostasis; (4) self-reflection; (5) dealing effectively with uncertainty in the domains of risk, ambiguity and intertemporal choice. Overall, we find a lack of research into how older people make economic and social decisions. There is, however, some evidence that older adults outperform young adults on certain subcomponents of wisdom, but the exact relationship between old age and each subcomponent remains unclear. A better understanding of these relationships holds the potential to alleviate a wide range of mental health problems, and has broad implications for social policies aimed at the elderly.

Keywords: aging, wisdom, decision making, social conflicts, emotion

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Introduction

"With age comes wisdom, but sometimes age comes alone."
—Oscar Wilde

World life expectancy has been steadily rising in the past two centuries and is expected to continue increasing for the foreseeable future (Oeppen and Vaupel, 2002). Increased longevity is especially pronounced in developed countries compared to developing ones (Mathers et al., 2001). Based on a steady increase of almost 3 months of life per year, it may not be uncommon for those born since 2000 in certain developed countries, such as USA, the UK, Japan and other western European countries, to live for 100 years (Christensen et al., 2009; Vaupel, 2010). This is astonishing given that the average life expectancy in developed countries was under 45 years in 1900 (Juvin, 2010). The population is also expected to continue to age rapidly over the next few decades (Lutz et al., 2008). There are serious economic and social implications of our increasing longevity and rapidly aging population (Schneider and Guralnik, 1990; Lloyd-Sherlock, 2000; Tinker, 2002; Poterba, 2004; Bloom et al., 2010b; see Bloom et al., 2010a).

The extra years of lives will need to be financed and there will be less people in the labor force than outside of it based on current retirement age laws (Sierra et al., 2009). The roles of social norms surrounding education, employment and retirement will need to be rethought so that the elderly can continue to contribute without impinging on the prospects of the younger citizens (Vaupel and Gowan, 1986; Vaupel and Loichinger, 2006).

Traditionally, research on aging has focused on the cognitive aspects of age-related changes. Old age is associated with declines in many aspects of cognition (reviewed in Hedden and Gabrieli, 2004; Raz and Rodrigue, 2006; Park and Reuter-Lorenz, 2009), as well as with a variety of detrimental stereotypes of incompetence (see Cuddy et al., 2005; Kite et al., 2005; North and Fiske, 2012). Recent major theories on aging, however, emphasize that emotion and motivation play a fundamental role in shaping age related changes in decision making and well-being. The Socioemotional Selectivity Theory (Carstensen et al., 1999) proposes that time horizons influence goals and people engage in a lifelong selection process of strategically and adaptively cultivating their social networks to maximize social and emotional gains and minimize social and emotional risks. When time is perceived as open-ended, goals are most likely to be preparatory and to be used to optimize the future, e.g., gathering information, experiencing novelty and expanding breadth of knowledge. As a result, young adults may place the greatest emphasis on the potential for information gain and future contact. When constraints on time are perceived, goals focus more on objectives that can be realized in their pursuit to maximize meaningful activities in the present. As a consequence, goals emphasize feeling states, particularly regulating emotional states to optimize well-being. Thus, elderly people tend to place the greatest emphasis on the potential for affective gain. Strength and Vulnerability Integration Theory (Charles, 2010) incorporates the socioemotional selectivity theory and further states that aging is associated with strengths in emotion regulation that entail the use of attentional, appraisal, and behavioral strategies of emotion, as well as vulnerabilities in emotion regulation as a consequence of reduced physiological flexibility, especially in situations that elicit high levels of sustained emotional arousal. The Motivational Theory of Life-Span Development (Heckhausen et al., 2010) proposes that individuals in late adulthood shift from primary control processes that are directed at changing the world by bringing the environment in line with one's wishes to secondary control processes aimed at changing the self to bring oneself in line with environmental forces. To meet the major challenges faced in old age, individuals need to increasingly resort to secondary control strategies of adjusting expectations, values, and attributions in order to pursue more attainable goals when certain primary control goals become unattainable. These theories suggest that aging is associated with dramatic changes in personal goals and highlight the strategies and skills used to achieve these new goals.

While aging is generally viewed as a "phenomenon of decline", there is an aspect to it that "holds more promise than present reality may reveal": wisdom (Baltes and Staudinger, 1993). The concept of wisdom has its roots in religion and philosophy (see Ardelt, 2004; Baltes and Smith, 2008). Wisdom is a complex, multi-faceted construct and there is no consensus on its definition, instead there are a variety, of mostly overlapping, theories of wisdom (Baltes and Staudinger, 2000). This has been largely encapsulated and distilled into six subcomponents by Meeks and Jeste (2009): (1) prosocial attitudes/behaviors; (2) social decision making/pragmatic knowledge of life; (3) emotional homeostasis; (4) reflection/self-understanding; (5) value relativism/tolerance; and (6) acknowledgment of and dealing effectively with uncertainty.

Despite empirical research into the construct of wisdom spanning more than three decades, the topic of wisdom continues to be overlooked by the neuroscience and psychology communities (Jeste and Harris, 2010) and only has gained attention in recent years in the field of aging-related research. This paper will review and connect the behavioral sciences and neuroscience literature on wisdom and aging, and will be organized around the theoretical framework of Meeks and Jeste (2009). For this review, we integrate the two subcomponents of (2) social decision making/pragmatic knowledge of life, i.e., knowing how to successfully navigate challenging social situations, and (5) value relativism, i.e., tolerance of another person's or culture's value systems, into one: "resolving social conflicts". Our rationale is that both of these subcomponents of wisdom are essential to making sound social decisions. We begin with a review of the literature on age differences in prosocial behaviors, specifically on experimental economic games.

Prosocial Behaviors

Wisdom entails the ability to achieve a common social good. Prosocial behavior broadly refers to acting beyond one's self-interest to benefit other people in one's social group and/or society (Penner et al., 2005). In economics, there are three major types of prosocial behavior: reciprocity, inequity aversion and altruism (see Fehr and Fischbacher, 2002). They are usually measured by the amount of a finite amount of money that is split with another person in experimental economic games. Reciprocity refers to responding in a similar manner to the actions of another person. This depends on the perception of (un)fairness of the actions of the other person, which is determined by whether split amounts are deemed equitable. Inequity aversion refers to wanting to achieve an equitable split of outcomes. This includes wanting to increase or decrease the amount allocated to another person who falls short or exceeds the equitable threshold respectively. Altruism refers to always, i.e., unconditionally, responding positively to another person's action. This means never wanting to decrease another person's allocated amount.

Standard economic theory assumes that "*all* people are *exclusively* motivated by their material self-interest" and thus, do not care about the well-being of others (Fehr and Schmidt, 1999). That is, players will maximize their self-interest at the expense of others—even in experimental games.

However, an overwhelming number of studies have consistently rejected this standard economic "self-interest hypothesis" and have provided evidence showing that individuals also have prosocial motivation (for reviews, see: Fehr and Schmidt, 2001; Meier, 2006; Levitt and List, 2007; Henrich et al., 2010). There are at least five common economic games to measure prosocial behavior: ultimatum, dictator, trust, prisoner's dilemma and public goods. These experimental games are traditionally played under complete anonymity (to the other player and the experimenter). Depending on the type of prosocial behavior of interest, these games may be played either one-shot, i.e., once, or repeated. These games differ in whether they are played simultaneously, i.e., players make their moves at the same time, or sequentially, i.e., players move one at a time and the move of a preceding player is known. In the next section, we will review older people's prosocial behavior on these games. Although there are numerous studies examining prosocial behavior on these games, only a handful have examined its relationship with old age. We will begin with a review of ultimatum game (UG)s (see **Figure 1A**).

Ultimatum Game

The classic UG is a two-player, sequential game that involves splitting a sum of money between a Proposer and a Responder (Güth et al., 1982). The Proposer is endowed with a fixed amount of money, say, \$10, and has to propose some amount, x, to another person, whose identity is not known. The Responder has two choices: accept or reject the proposed offer. If the offer is accepted, the Responder gets x, while the Proposer gets \$10-x; if the offer is rejected, both players receive nothing (See Thaler, 1988, for a readable description of the common UG variations). The standard economic "self-interest hypothesis" predicts that the Proposer will offer the minimum amount possible (e.g., one cent), which would be accepted by the Responder who values this over nothing. However, this is very rarely the case (see Güth and Tietz, 1990; Güth, 1995; Cooper and Dutcher, 2011; Güth and Kocher, 2014). A meta-analysis of 37 papers found that, on average, Proposers offered 40% of their "pie", i.e., endowment, to Responders (Oosterbeek et al., 2004). Offers for larger pie sizes and shares tend to be rejected less often (Oosterbeek et al., 2004); many studies report that it is not uncommon for offers of less than 40–50% of the pie to be rejected (see Cooper and Dutcher, 2011). This willingness to punish unfair behavior while incurring a cost reflects the degree of social inequity aversion.

We report a total of five studies that examine the prosocial behavior of older people on UGs. Two studies examined age differences for Proposers and reported different results. One study found that older participants proposed more generous offers than younger participants in the standard UG (Bailey et al., 2013), while another found no age differences (Beadle et al., 2012). Studies examined age differences for Responders' acceptance/rejection rates with mixed results. Two studies did not find any age differences (Beadle et al., 2012; Bailey et al., 2013). One study reported no difference for fair (50% of the pie) and unfair (10% and 20% of the pie) offers but older participants were more likely to reject moderately unfair (30% of the pie) offers (Harlé and Sanfey, 2012). It was found that older participants rejected more unfair offers (Roalf et al., 2012). When the unfairness was self-advantageous, older participants were more likely to reject very high offers, which suggests inequity aversion since they do not want to be unfair to the other party (Bellemare et al., 2011).

Overall, older participants exhibit at least equal, or perhaps even more, prosocial behavior as Proposers. As Responders, older people appear to display greater inequity aversion, even in self-advantageous conditions.

Dictator Game

The classic dictator game (DG; see **Figure 1B**) is similar to the UG, except that the Responder cannot reject, and must accept, the amount offered by the Proposer, i.e., the "dictator" (Kahneman et al., 1986; Forsythe et al., 1994). The standard economic "self-interest hypothesis" predicts that the Proposer will offer nothing. However, a meta-analysis of 129 experiments reported that 63.89% of participants offered a positive amount with an average of 42.64% of the pie, while 36.11% offered nothing (Engel, 2011). Further, age had "a strong effect": giving nothing decreased with age and "never happens in the elderly", who give at least 50% of the pie almost all of the time (Engel, 2011). It is also worth reporting the results of three other studies that specifically examined the relationship between prosocial behavior on DG and older people. These studies were published after the meta-analysis. Two studies did not find any significant relationship (Roalf et al., 2012; Rieger and Mata, 2015). The other study used a modified DG by inducing empathy into dictators and found older people to give significantly more (Beadle et al., 2013).

Overall, older people seem to exhibit more prosocial behavior in the DG. It is worth highlighting a surprising finding from the meta-analysis: the mode for elderly contribution was 100% of the pie (Engel, 2011). However, more studies are needed to investigate age differences in the DG since 94.7% of dictators in the meta-analysis were students and only 0.7% was elderly people.

Trust Game

The classic trust game (TG; see **Figure 1C**) is a two-player, sequential game that involves splitting a sum of endowed money between an Investor and Trustee in two stages (Berg et al., 1995). In the first stage, both players are endowed with a fixed amount of money, say, \$10, which the Investor can choose to invest or keep. If the Investor chooses to keep the money, the game ends. If the Investor chooses to invest, then an amount, x, must be specified. This amount, x, is then tripled by the experimenter so that the Trustee receives $3x$ In the second stage, the Trustee can decide whether to return the money to the Investor. If the Trustee decides to keep the money then the game ends with the Investor having a total of \$10$-x$ and the Trustee, \$10 + $3x$ If the Trustee chooses to return some money, y, then the game ends with the Trustee

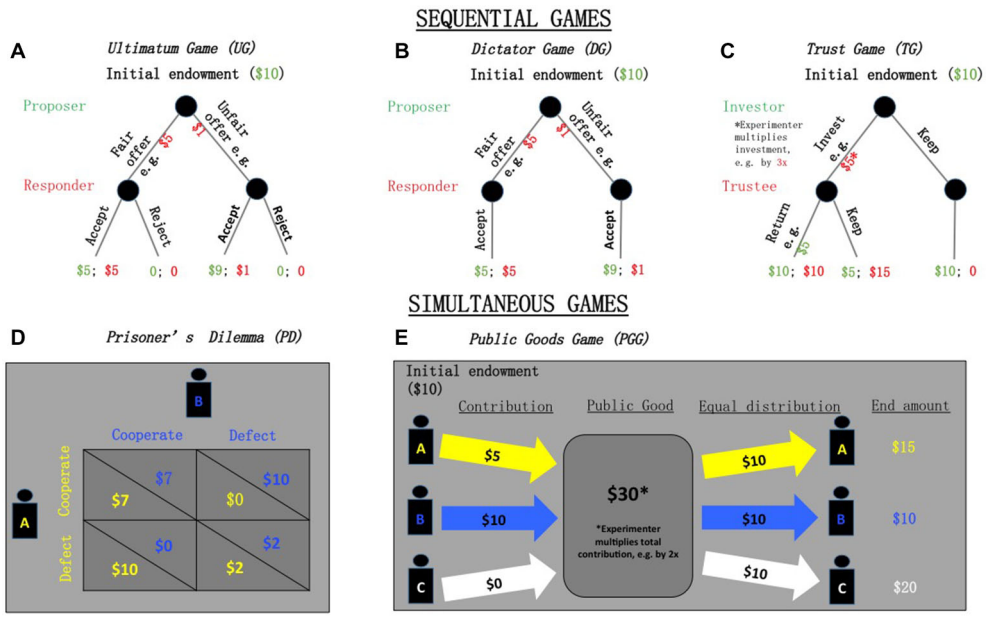

FIGURE 1 | The behavioral game paradigms. In sequential games, such as the ultimatum game (UG) **(A)**, dictator game **(B)**, and trust game **(C)**, games are played sequentially, i.e., players move one at a time and the move of a preceding player is known. In simultaneous games, such as prisoner's game **(D)**, and public goods game **(E)**, players make their moves at the same time.

earning a total of \$10 + $3x$ −y and the Investor, \$10−x+y. However, in many replications of game, the Trustee is not endowed with any money at the beginning (Johnson and Mislin, 2011).

The TG can be viewed as a variant of the DG, where the Trustee dictates an amount that was initially allocated by the Investor (Camerer and Fehr, 2004). The standard economic "self-interest hypothesis" predicts that no money will be invested since the Investor will anticipate the Trustee keeping all of the investment and not returning anything. This hypothesis is, however, not supported by empirical findings. A meta-analysis of 162 experiments involving more than 23,000 participants found Investors to invest 50% of the endowment on average, and Trustees to return 37% of the total amount they had available (Johnson and Mislin, 2011).

Individual studies examining the relationship of older people's prosocial behavior on TGs report mixed results. Three studies found no significant relationship for amount invested and amount returned by Trustees (Etang et al., 2011; Johansson-Stenman et al., 2013; Rieger and Mata, 2015). One study found older people to invest and return more (Sutter and Kocher, 2007). Three studies found older people to invest less, of which two found older people to return more (Fehr et al., 2003; Bellemare and Kröger, 2007), while the other did not measure this relationship (Holm and Nystedt, 2005). The meta-analysis did not examine age but found students to return less money compared to non-students and no difference for amount invested (Johnson and Mislin, 2011), which could suggest that older people invest more since non-students are generally older than students.

Overall, there is no clear evidence on the prosocial behavior of older people playing TGs based on the seven studies reviewed. Of the seven studies that examined Investor behavior, three found no significant relationship with age, three found a negative relationship and one found a positive relationship. Six of the seven studies examined Trustee behavior and half found no significant relationship with age while the other half found a positive relationship.

Prisoner's Dilemma

The classic prisoner's dilemma (PD; see **Figure 1D**) is a two-player, simultaneous game where each player can either choose to cooperate or defect. How much each player earns depends jointly on the choices made by both players. There are three possible scenarios with their respective payoffs in parentheses, where a larger number represents a higher payoff: one player cooperates while the other defects (1:4), both players cooperate (3:3), and both players defect (2:2).

The PD tests whether players reciprocate expected cooperation (Camerer and Fehr, 2004). The standard economic "self-interest hypothesis" predicts that each player will choose to defect, which would lead to both players earning the second lowest payoff. Although mutual cooperation would lead to the second best outcome, there is the possibility of earning the worst payoff if the other player defects. This is also known as the Nash equilibrium: both players can do no better in terms of payoffs than to defect (Nash, 1951). However, there is overwhelming evidence of cooperation in experimental PD games (Dawes, 1980; Sally, 1995; Cooper et al., 1996; Brosig, 2002; Jones, 2008; Balliet, 2009).

Although the PD is one of the most well-known games, there are no studies examining the performance of older people. We identified 124 unique PD studies from four meta-analysis studies (Balliet, 2009; Balliet et al., 2009, 2011a,b). Of the 119 studies that we could access, 108 used student samples (90.7%). The remaining 11 studies either did not report age, or had a mean age of <37 years old. More studies involving older participants are required for a better understanding of their performance on PD.

Public Goods Game

The classic public goods game (PGG; see **Figure 1E**) is a generalized form of PD involving multiple players. Players are endowed with some amount of money, which they can choose whether to contribute to a "public good" or not. If players contribute (cooperate), the sum of contributions are multiplied by some factor, *m*, and distributed evenly to all players, including those who did not contribute. If players do not contribute (defect), they keep their money and stand to gain from the distribution based on the contribution of other players.

While the group would benefit most if everyone contributed, the standard economic "self-interest" hypothesis predicts no contribution at all. This hypothesis, is however, not supported by empirical findings (Ledyard, 1995; Chaudhuri, 2011). A meta-analysis of 27 studies involving 711 groups of participants found the average contribution to be 37.7% of the total endowment (Zelmer, 2003). Only one study examined the relationship between older people's prosocial behavior in a PGG and it reported a concave result, i.e., the middle-aged participants contributed the most compared to older and younger participants (Rieger and Mata, 2015). More studies involving older participants are required for a better understanding of their performance on PGG.

Competitive Behavior

The willingness and ability to compete is usually important for the economy. It has been suggested that prosocial tendencies increase while competitive behavior declines with older age (see Mayr et al., 2012). There are three behavioral experiments that examine competitive behavior in old age (Charness and Villeval, 2009; Mayr et al., 2012; Sproten and Schwieren, 2015). In these experiments, participants are given a task, e.g., simple mental arithmetic, and the choice of payment based on absolute or relative performance. Choosing to be paid based on performance relative to other participants and doing well reflects a willingness and ability to compete respectively. Two of the three studies found no significant age differences in willingness to compete (Charness and Villeval, 2009; Sproten and Schwieren, 2015), while the other found an inverted U-shaped relationship: willingness increased up to 50 years old and declined after Mayr et al. (2012). All three studies report no significant age differences in ability to compete. Taken together, these findings mostly suggest that older people remain willing and able to compete.

Summary

We surveyed the literature on the prosocial behavior of elderly people across five common types of experimental games. Results were mixed and there was no clear evidence of age differences in prosocial behavior across these games. We also identified several important issues consistent across games that need to be addressed in the future. First, there are only a few studies involving older participants. For some games such as PD, there were no studies examining age differences. Second, most of these studies involve small samples, e.g., 18 young adults vs. 20 older adults (Harlé and Sanfey, 2012). Third, there were many sources of heterogeneity across studies. There were differences in whether studies employed a between- or within-subjects design and controlled for confounding factors such as income, as well as the average age of participants and in the design of the games, e.g., one-shot vs. repeated, amount endowed, etc. We also surveyed the literature examining the competitive behavior of older people in experiments where participants can choose to be paid based on absolute or relative performance. Overall results from three studies suggest that older people generally remain willing and able to compete.

Resolving Social Conflicts

The ability to resolve social conflicts can be viewed as possessing social wisdom and refers to recognizing and respecting differences in individuals' value systems and employing pragmatic reasoning to successfully navigate social issues in life with a preference for compromise (Basseches, 1980; Kramer, 1990; Baltes and Smith, 2008). There is empirical evidence that social wisdom improves with age. Older people tend to use more complex reasoning schemas that emphasize multiple perspectives and compromise when faced with various social dilemma scenarios (Grossmann et al., 2010). However, gains in social wisdom may be influenced by cultural differences in the socialization of interpersonal harmony and conflict avoidance. For example, there were age differences in social wisdom between Japanese and American adults, but this depended on whether the dilemma was interpersonal or intergroup (Grossmann et al., 2012). Further, contrary to the adage "with age comes wisdom, a recent study found no age differences in wise reasoning about personal conflicts in American adults (Grossmann and Kross, 2014). Moreover, both younger and older adults exhibited similar amounts of the self-distancing effect, i.e., reasoning more wisely about other people's social problems than about their own. The lack of age-related difference in wise reasoning was also observed in another study, which asked participants about nonthreatening, but still rather age-neutral area of the self, e.g., "Please think aloud about yourself as a friend" (Mickler and Staudinger, 2008). These findings suggest that social wisdom may not be a universal and homogenous construct, and highlight the need for more studies on samples from different countries and cultures.

Everyday problem-solving/decision-making effectiveness (EPSE) is another domain that involves resolving social conflicts. EPSE incorporates both real world decision making and everyday problem solving abilities (see Thornton and Dumke, 2005). EPSE tasks typically assess the number of "safe and effective" solutions participants can generate to everyday social problems, e.g., "What should an elderly woman who has no other source

of income do if her social security check does not come in 1 month?" (Heidrich and Denney, 1994). A higher number of solutions generated reflects greater EPSE. A meta-analysis of 28 studies ($N = 4482$) found an overall decline in EPSE among older participants (Thornton and Dumke, 2005). Moderator analyses revealed that age differences in EPSE were substantially reduced when problems were interpersonal and when older adults were highly educated (Thornton and Dumke, 2005). We also found that most, if not all, of the 28 studies were conducted in Anglo countries.

Emotional Homeostasis

Successful emotion regulation that maintains emotional homeostasis is crucial to wisdom. Old age is generally perceived as "Doom and gloom", which characterizes later life as a time of profound physical, cognitive, and emotional declines. Yet recent empirical and theoretical work challenges this view by illustrating the "bright side" of aging. Accumulating evidence shows that older adults attend to and remember positive vs. negative information to a greater extent than younger adults (Mather and Carstensen, 2005). A recent meta-analysis of age-related positivity effect confirmed that older adults show a significant information processing bias toward positive, but not negative, information (Reed et al., 2014). In corroborating with these behavioral evidence, recent neuroimaging studies found a relative reduction in activation during loss anticipation paralleled by significantly weaker negative arousal for large loss cues in older adults, despite intact striatal and insular activation during gain anticipation with age (Samanez-Larkin et al., 2007). Healthy older adults also exhibited enhanced activity in the nucleus accumbens in response to an expected reward value (Chowdhury et al., 2013). A recent neuroimaging study demonstrated that responsiveness to regret was specifically reduced in successful aging paralleled by autonomic and frontostriatal characteristics indicating adaptive shifts in emotion regulation, suggesting that disengagement from regret reflects a critical resilience factor for emotional health in older age (Brassen et al., 2012). Taken together, recent research indicates that older adults may outperform younger adults in maintaining emotional homeostasis, which might contribute to their wisdom in dealing with life challenges.

Self-Reflection

The concept of self is very complex and includes various types of self-directed internal thought processes including autobiographical reminiscence, self-referencing, self-esteem, and so on. The ability to reflect on self is an essential prerequisite for insight. To date, the vast majority of studies examining age-related changes in self-understanding have focused on self-referential processes. Self-referential processing takes place when an individual encodes information into memory in reference to the self (Rogers et al., 1977; Symons and Johnson, 1997). Recent behavioral studies found that self- and close other-referencing similarly enhance memory for both young and older adults relative to the distant other people condition, suggesting that self-referencing provides an age-equivalent boost in memory (Hamami et al., 2011). Other studies found that elderly subjects were lower on self-consciousness and their pattern of recall was similar for self- vs. other-referenced items. Neuroimaging studies have demonstrated that the default network regions such as medial prefrontal cortex and posterior cingulate gyrus are implicated in the processing of self-relevant social information (Gusnard et al., 2001; Martinelli et al., 2013). The default network is engaged during baseline rest periods when participants are not focused on task-directed thought and is suppressed during attention-demanding tasks (Raichle et al., 2001). Aging also alters the neural activity associated with the successful formation of memories for self-referenced information (Gutchess et al., 2010). Future studies need to directly link changes in self-understanding and performance in social problem solving and personal well-being.

Dealing Effectively with Uncertainty

Decisions often need to be made in situations of risk and ambiguity, i.e., uncertainty. Dealing with such situations effectively is a crucial component of wisdom. In decision theory, a distinction is made between risk and ambiguity based on whether the probability associated with an outcome is known. If the objective probability of an outcome is known, it is risky; if the objective probability of an outcome is not known, it is ambiguous (Tversky and Fox, 1995). The two classic economic theories for understanding decisions under risk and ambiguity are expected utility (EU) and subjective expected utility (SEU). In EU (Morgenstern and Von Neumann, 1947), outcomes are evaluated based on their objective probabilities. In SEU (Savage, 1954), objective probabilities may not be known and outcomes are evaluated based on the decision maker's subjective probabilities of outcomes. In both theories, decision makers multiply the probabilities and values associated with outcomes and choose the outcome that yields the greatest expected value. Attitudes towards risk and ambiguity are generally classified as "aversion" or "seeking". Risk aversion is defined as preferring a less risky outcome to a more risky outcome with equal or greater expected value (Rabin and Thaler, 2001), e.g., choosing between $10 for sure and a 50% chance to win $20 or nothing. Conversely, risk seeking is defined as preferring a more risky outcome to a less risky outcome with equal or greater expected value. Ambiguity aversion is defined as preferring outcomes with known probabilities to outcomes with unknown probabilities; conversely, ambiguity seeking is defined preferring outcomes with unknown probabilities to outcomes with known probabilities (Epstein, 1999).

Risk

Risky choices are usually elicited in laboratory experimental settings using a variety of behavioral tasks. These tasks can be classified as requiring decision makers to make their *decisions from description* or *experience* (Hertwig et al., 2004). In tasks requiring decisions from description, options are described with

their outcomes and probabilities. In tasks requiring decisions from experience, these descriptions are not explicitly provided and decision makers instead rely on personal experience from making previous similar choices.

An example of a task requiring decisions from description would be choosing between $10 for sure and a 50% chance to win $20 or nothing. A large number of studies investigating risk employ this approach (Weber et al., 2004). However, this approach has been criticized on the grounds of being an unrealistic representation of typical real world situations where summary descriptions of choice outcomes and probabilities are not provided (Hertwig et al., 2004). Instead, it was argued, tasks requiring decisions from experience are more reflective of everyday life (Hertwig et al., 2004). An example of such a task would be repeatedly choosing between outcomes sampled from unknown probability distributions and this is usually done on a computer. It is worth noting that decisions from experience contain a degree of uncertainty, i.e., it is not strictly uncertain because the statistical probability can be estimated (see Rakow and Newell, 2010). Intuitively, one would expect choices to be similar on both tasks when payments are the same on average. However, this is not the case: on a decision from description task, the modal choice tends to be the risky option while the sure outcome tends to be preferred on a decision from experience task (see Hau et al., 2008; Rakow and Newell, 2010). This difference in risky choice is known as the *description-experience gap*. Several explanations for this gap have been proposed (for a review, see Hertwig and Erev, 2009).

A meta-analysis of 29 studies (N = 4093) using various behavioral tasks to investigate age differences in risky decision making reported mixed results (Mata et al., 2011). There was no overall significant age difference in tasks involving decisions from description although age differences varied across individual tasks. On tasks involving decisions from experience, there was a significant overall age difference: older adults were slightly more risk seeking (d = 0.28). However, age differences varied across individual tasks. Combining tasks involving both decisions from experience and description yielded a negligible age difference (d = 0.07). The authors conclude that "different tasks characteristics engender age-related differences in risky choice" (Mata et al., 2011).

Ambiguity

An ambiguity-averse individual would rather choose an alternative where the probability distribution of the outcomes is known over one where the probabilities are unknown. Regarding uncertain outcomes, people are generally believed to display ambiguity aversion (Camerer and Weber, 1992; Keren and Gerritsen, 1999). However, there is a dearth of studies examining age differences in decision making in ambiguous situations. One study found no significant age differences in gambles (Kovalchik et al., 2005), while another found older participants to be less ambiguity-averse in gambles (Sproten et al., 2010) i.e., they were more likely to choose the ambiguous outcome to the certain outcome. The lack of studies could be due to the general difficulty in measuring pure ambiguity in laboratory experiments (Lopes, 1983). As such, more studies investigating how older people make ambiguous choices are needed.

Intertemporal Choice

Wisdom is required to make good decisions about future life plans and goals (Baltes and Smith, 2008). Many important life decisions require making intertemporal choices, i.e., trading off time and outcomes such as money, health or happiness. For example, deciding whether to pursue higher education while earning little to no money over a few years for a potentially greater lifetime earnings in the future (Read et al., 2013). Intertemporal choices involve ambiguity since the future is uncertain (Read and Read, 2004). In experiments, participants are typically asked to choose between smaller-sooner (SS) and larger-later (LL) amounts of money, e.g., $100 today or $110 in 1 year. Standard economic theory assumes exponential, i.e., constant per period, discounting, although this is not supported by empirical evidence, which suggests that individuals tend to be impatient, i.e., they prefer SS outcomes, and discount future outcomes more (Frederick et al., 2002).

Fourteen studies examined the relationship between impatience and age.[1] Half studies found older people to be more patient (Green et al., 1994; Harrison et al., 2002; Reimers et al., 2009; Whelan and Mchugh, 2010; Löckenhoff et al., 2011; Halfmann et al., 2013; Li et al., 2013). Four studies found no difference (Chao et al., 2009; Samanez-Larkin et al., 2011; Roalf et al., 2012; Rieger and Mata, 2015). Two studies found older people to be more impatient (Green et al., 1996; Albert and Duffy, 2012).[2] Finally one study found a curvilinear relationship with middle-aged people the most patient, while older people were more impatient than younger people (Read and Read, 2004). The only two studies that investigated intertemporal discounting on losses both found no age effects (Löckenhoff et al., 2011; Halfmann et al., 2013).

There are several possible explanations for the discrepancies in results across studies. For example, Read and Read (2004) pointed out that an earlier study by Green et al. (1994) focussed on incomparable samples, which were quite small (n = 12 per group), without controlling for confounding factors such as income, etc. Similar criticisms may apply to more recent studies as well (e.g., Whelan and Mchugh, 2010; Samanez-Larkin et al., 2011; Halfmann et al., 2013). Rieger and Mata (2015) proposed another reason for their finding of no age effects in 700 Moroccans: age differences may not generalize across cultures and nationalities. Another reason pointed out by Li et al. (2013) is the difference in the average age of older participants across studies, with few studies having sufficient data for participants above 65 years old.

Finally, we noticed large differences in the questions asked across studies. For example, monetary amounts offered ranged

[1]Studies either measure the discount rate or impatience but holding the amounts and time constant, a higher discount rate implies greater impatience.
[2]To be precise, Green et al. (1996) found lower income adults more impatient than upper income younger adults but no differences between upper income younger and older adults.

from less than $10 to $1800 and the interval length between SS and LL varied from a few days to weeks, months and even years. Studies have found impatience to be influenced by the magnitude of the outcome, the interval length between outcomes and the delay from the present to the availability of the outcomes (e.g., Thaler, 1981; Kirby et al., 1999; Read, 2001; Read and Roelofsma, 2003). These factors may influence people of different ages differently, although no studies have examined this yet. There were also few studies investigating age differences and intertemporal choices involving losses.

Summary

Taken together, these studies revealed that age-related changes in economic decisions involving risk, ambiguity, and intertemporal choices are determined by task characteristics, the specific age range, and a variety of other methodological factors (Frederick et al., 2002; Mata et al., 2011). There is insufficient evidence to accurately determine whether older adults make risky, ambiguous and intertemporal choices differently from younger adults.

Concluding Remarks

Overall, the relationships between age and each of the subcomponents of wisdom remain unclear. This is a relatively young field, and it is still a challenging prospect to integrate the conflicting findings often found in this field. Several issues may contribute to the inconsistency in findings. First, there were differences in the average age across studies, with few studies having sufficient data for participants above 65 years old. For studies that used a between-subjects design, the average age for both the older and younger, i.e., comparison, group of participants could differ substantially across studies. Second, there were significant methodological variations across studies. Studies differed in the types of task used, study designs employed and in controlling for potential confounding factors. Third, a number of studies, especially in the neurosciences, used small sample sizes, which undermines the reliability of the findings due to a lack of statistical power (Button et al., 2013). These issues have been consistently documented in the aging literature (Rhodes, 1983; Kite and Johnson, 1988; Thornton and Dumke, 2005; Ng and Feldman, 2008).

We also uncovered several gaps in the literature that future research can address. First, participants in most of the studies were mainly from Anglo countries. This is consistent with findings from Henrich et al. (2010) who questioned generalizability of behavioral science findings across human populations due to the overwhelming number of studies on student samples from Western, Educated, Industrialized, Rich and Democratic countries, and in particular USA. The need for non-Anglo samples is relevant given the finding of age-related differences in social wisdom between Japanese and American adults (Grossmann et al., 2012). Second, there is a lack of research into how factors such as gender, individual differences in personality, culture and the environment influence wisdom in the elderly. Third, studies typically employed cross-sectional and not longitudinal designs, which is in line with other fields examining age differences (Rhodes, 1983; Ng and Feldman, 2008). This results in cohort effects (Rhodes, 1983), which threaten the internal validity of studies and limit our understanding of age-related changes in the subcomponents of wisdom over the lifetime.

There is a compelling need for future studies to address the aforementioned issues in order to better understand how older people make economic and social decisions. This is especially important given the impending demographic shift to an older society. The prejudice and stereotypes may limit meaningful participation in society, e.g., jobs, and affect the mental health states of old people, who may even internalize and play into the stereotypes in self-fulfilling prophecies (Taylor and Walker, 1994, 1998; Levy, 2001; Coudin and Alexopoulos, 2010). A better understanding of the actual changes in old age can help foster a more inclusive society that taps on the expertise and skills of those older. This in turn may help alleviate feelings of social isolation, loneliness and depression (Perlman and Peplau, 1981). Understanding these issues is pertinent to implementing early interventions aimed at preventing a wide range of mental health problems, and has broad implications for social policies aimed at the elderly.

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frontiers in Aging Neuroscience

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Memory impairment in older adults' diversionary thoughts

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The diversion paradigm was created in the context of explaining the effect of the instruction to forget some recently encoded material in the list-method of the directed forgetting paradigm. The current study of healthy older adults employed the diversion paradigm with two main goals: to determine whether thinking about an autobiographical memory interferes with the recall of recently encoded information and to explore whether the degree of forgetting depends on the temporal distance created by the diversionary thought. Ninety non-institutionalized Portuguese older adults (47 females and 43 males), aged 65–69 years, with education levels of between 3 and 6 years participated in this study. The exclusion criteria were as follows: presence of depressive symptomatology (assessed with the Geriatric Depression Scale-30) and global cognitive deterioration (assessed with the Mini–Mental State Examination). Concerning the diversion paradigm, one group was instructed to think about an autobiographical event (remembering one's childhood home or the last party that one had attended) after studying one word list (List 1) and before viewing the second word list (List 2). After a brief distraction task, the participant had to recall the words from both of the studied lists. In the control group, the procedure was the same, but the diversionary thought was substituted by a speed reading task. The obtained results showed the amnesic effect of diversionary thought but did not show a greater degree of forgetting when the autobiographical events in the diversionary thoughts were temporally more distant. Considering the practical implications of these results, this study alerts us to the importance of promoting strategies that enable older adults to better remember important information and effectively forget irrelevant information.

Keywords: diversion paradigm, older adults, amnesic effect, autobiographical memories, free recall

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Introduction

Certainly, many of us have experienced boring or uninteresting contexts in our lives that have led our minds to journeys into the past, present or future that are full of idyllic images and that concern moments, problems or fantasies (Klinger, 1978). Who does not remember that time when the classroom teacher told us not to be distracted and to stop daydreaming? Actually, we were not distracted; we were only shifting our mind's focus to a different mental context induced by the mind's wandering or a mental diversion (Sahakyan and Kelley, 2002). Diversion thinking refers to off-task thoughts; in other words, our attention is dissociated from the current context and attached to the mind's wandering context (Smallwood and Schooler, 2006). Returning to the classroom after our mini mental journey, we attempt to remember the

information that we acquired before we began to wander, and we acknowledge the difficulty of recalling this information. The amnesic effect of daydreaming has occurred (Delaney et al., 2010).

Forgetting is commonly believed to be problematic, especially in the aging context. Its importance is underestimated, and it is viewed as a memory failure (Sheard and MacLeod, 2005). However, scientific evidence indicates that human beings have structures for suppressing irrelevant information, disallowing the buildup of information interference and improving learning and retrieval abilities (e.g., Hasher et al., 1999; Anderson and Craik, 2000). Forgetting is essential to an efficient memory system (Bjork et al., 2006), and it has been widely studied using the directed-forgetting paradigm (e.g., Bjork, 1970, 1989; Johnson, 1994; MacLeod, 1998). This paradigm has two procedures: the list method and the item method. In the item method, the forgetting instruction is given item-by-item (e.g., Basden and Basden, 1996; MacLeod, 1999; Sahakyan and Foster, 2009). By contrast, the list method employs the forgetting instruction after a whole list—generally, the first list—has been presented. The main result of these procedures shows contrasting memory performance for the to-be-forgotten items vs. the to-be-remembered items: lower recall is observed for the to-be-forgotten items in comparison with the recall level of the to-be-remembered items.

Sahakyan and Kelley (2002) developed the diversion paradigm to explain how participants in a directed forgetting paradigm with the list method comply with the instruction to forget some recently presented material. In this paradigm, after learning the first list, the participants are instructed to engage in diversionary thought (e.g., thinking about their parents' home or imagining being invisible). With these instruction modifications that explicitly command the mind's focus to another mental context, it was observed that both younger and older adults showed significant forgetting (Sahakyan et al., 2008). One explanation for the diversion paradigm effect (the impaired ability to retain the information acquired immediately before the diversionary thought) claims that diversionary thought begins a new mental context in which the items on the second list are encoded and that, in this way, the context of the first list study becomes quite different from the context of the memory test (Sahakyan and Delaney, 2005; Delaney et al., 2010). It is also important to observe that accepting the contextual account does not necessarily imply discarding the possibility of the inhibition intervention. The contextual mental shifts (diversionary thought) might be followed by the inhibition of the unwanted context in which events were encoded (Anderson, 2009).

According to Delaney et al. (2010), it is important not only to study how diversionary thought contributes to forgetting information—which the authors call the amnesic effect of diversionary thought—but also to estimate the magnitude of the diversionary thought effect depending on the mental distance (temporal, circumstantial, spatial) from the current moment. With this aim, the authors conducted two experiments with undergraduate students that included different diversionary thoughts about autobiographical memories: the students' parents' home vs. their current home (Experiment 1) and international vs. domestic vacations (Experiment 2). The study results showed worse recall of the first word list when the diversionary thought condition differed greatly from the participants' real situations in both space and time (long-distance vacations; their parents' home) in comparison with the condition in which participants thought about events that were current or nearer in space.

The present study employed the diversion paradigm developed by Delaney et al. (2010) in a sample of healthy older adults. The study has two aims: to determine whether thinking about an autobiographical memory interferes with the recall of recently encoded information and to explore whether the temporal distance implied by diversionary thought has an effect on the level of forgetting, specifically, with older thought events leading to more forgetting. We were specifically interested in learning whether thinking about autobiographical memories related to recent events (the last party the participant had attended) triggered less forgetting than did personal memories concerning a distant event (the participants' childhood home).

Materials and Methods

Subjects

Ninety community-dwelling older adults have voluntarily participated in this study. They were recruited through snowball sampling. The participants were assigned to one of the following conditions: experimental (two diversionary thought tasks, $N = 30$ each) or control (speed reading task, $N = 30$). Participants living in their childhood home were excluded from this study, as were those with a performance of more than 1 SD below the normal score on the Mini–Mental State Examination (MMSE; Folstein et al., 1975; Portuguese norms by Morgado et al., 2009) and the Vocabulary subtest of the Wechsler Adult Intelligence Scale 3rd edition; Wechsler, 2008). To rule out the presence of depressive symptomatology, participants with a score above 10 points on the Geriatric Depression Scale (GDS 30 item version; Yesavage et al., 1983; Portuguese adaptation and norms by Barreto et al., 2008) were excluded from the study. This study was approved by the Scientific Council of the Faculty of Psychology and Educational Sciences of the University of Coimbra, and verbal informed consent was obtained from participants prior to the session.

Materials

Delaney et al. (2010) diversion paradigm was adapted to Portuguese older adults. Two lists were created, each with 16 unrelated concrete Portuguese nouns selected from the Corpus for European Portuguese norms (Nascimento et al., 2009). Written frequency of the stimuli was medium to high according to the same norms. The words were read sequentially, keeping a card with the word visible, at a rate of 5 s per word. Each list served as List 1 and List 2 an equal number of times. The experimental condition concerning the diversion paradigm included two diversionary thought tasks: the participants' childhood home (old event condition) and the last party they had attended (recent event condition). The design of this experiment was a between-subjects design.

Procedure

The experiment began with the administration of the diversion paradigm (Delaney et al., 2010). All participants were tested individually and instructed to study two word lists (List 1 and List 2) for a later memory test. After studying List 1, the participants in each experimental group were asked to perform, within 45 s, one of the two diversionary thought tasks, whereas those in the control group performed a speed reading task (reading an excerpt about a collage technique aloud as quickly as possible while ignoring its content). The text selected for the reading control task did not include any of the words on the word lists. In the diversionary thought task, participants were asked to remember their childhood home, imagining themselves there and describing their home aloud (old event condition) or doing the same for the last party they had attended (recent event condition) in accordance with their condition assignments. Then, all participants studied the second list of words followed by an arithmetic filler task of backwards counting for 90 s. At the end, the participants were asked to freely recall the maximum number of words from each list on separate sheets of paper. First, they recalled the words from List 1 and then the words from List 2. The amount of time allotted for each list recall was 80 s. A post-experiment questionnaire concerning the diversionary thought (e.g., How often do you remember/think about your childhood home? Apart from the current situation, how much time had elapsed since the last time you had thought about or remembered your childhood home?) was applied. Later, the participants were also administered the MMSE to screen for their general cognitive functioning, the Vocabulary subtest of the Wechsler Adult Intelligence Scale 3rd edition to briefly assess their verbal skills, and the GDS 30 to evaluate the presence of depressive symptomatology. As the exclusion criteria were also based on the results on these tests, 9 subjects were eliminated from the present study. This procedure left a total of 90 participants.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 18 for Windows (IBM, New York, USA). The level of significance adopted for all the statistical comparisons reported was set at $p < 0.05$. We computed a one-way analysis of variance (ANOVA) for unrelated samples for the comparisons between the control and experimental conditions concerning the results on the MMSE, GDS 30 and Vocabulary test, and the same statistical test was calculated with condition (diversionary thought about an old event, diversionary thought about a recent event, and no diversionary thought) as the independent variable for the comparison concerning the words recalled from List 1 and List 2 in each experimental condition and control condition.

Results

Ninety non-institutionalized healthy older adults (47 females and 43 males) aged 65–69 years (M = 66.90, SD = 1.53), with education levels between 3 and 6 years, participated in this study.

TABLE 1 | Cognitive status, depressive symptomatology and vocabulary scores of the participants in the experimental and control conditions.

	Experimental conditions				Control condition	
	The childhood home		The last party			
	M	*SD*	*M*	*SD*	*M*	*SD*
MMSE	27.63	1.35	28.43	1.33	28.13	1.33
GDS-30	6.70	2.26	5.80	2.02	6.53	1.93
Vocabulary	37.27	9.35	38.77	8.39	39.73	9.28

The scores on the tests that were administered to assess the exclusion criteria for participants in this study are displayed in **Table 1**. The participants in the experimental conditions and in the control condition did not differ: $F_{(2,87)} = 2.74$, $MSE = 4.900$, $p = 0.070$, $\eta_p^2 = 3.195$ for the MMSE; $F_{(2,87)} = 1.60$, $MSE = 13.756$, $p = 0.208$, $\eta_p^2 = 0.059$ for the GDS 30 items; and $F_{(2,87)} = 0.57$, $MSE = 46.344$, $p = 0.568$, $\eta_p^2 = 0.013$ for the Vocabulary test.

The mean proportions of words recalled from List 1 and List 2 in each experimental condition (old event: the childhood home, recent event: the last party) and control (no diversionary thought) are presented in **Table 2**.

The ANOVA results indicated that condition significantly influenced the level of recall for List 1, $F_{(2,87)} = 6.44$, $MSE = 0.045$, $p = 0.003$, $\eta_p^2 = 0.124$. Games-Howell *post hoc* tests revealed significant differences between the old event (childhood home) condition and the control condition ($p = 0.020$) and between the recent event (last party) condition and the control condition ($p = 0.008$) but not between the old event condition and the recent event condition ($p = 0.978$). Thus, the amnesic effect of the diversionary thought was achieved. However, we did not find an effect of the event temporal distance produced by the diversionary thought, as the recall between the two experimental conditions did not differ. Concerning the List 2 recall, the ANOVA result was not statistically significant, $F_{(2,87)} = 1.65$, $MSE = 0.023$, $p = 0.198$, $\eta_p^2 = 0.037$, suggesting that the participants' recall levels were equal in the three conditions.

Discussion

In this study, the participants in both diversionary thought conditions recalled fewer words from List 1 than did participants in the condition with a reading speed task (control condition). Thus, remembering a personal past event produced recall impairment with the first studied word list, i.e., the expected amnesic effect of diversionary thought was achieved. The

TABLE 2 | Proportion of correct recall of both lists for experimental and control conditions.

	List 1		List 2	
	M	*SD*	*M*	*SD*
Experimental conditions				
The childhood home	0.14	0.09	0.22	0.11
The last party	0.13	0.07	0.21	0.15
Control condition	0.20	0.09	0.21	0.15

temporal distance of the diversionary thought (old event *vs* recent event conditions) did not influence recall; that is, the difference in List 1 recall levels between the two diversionary thought conditions did not reach statistical significance.

The first result concerning the amnesic effect of diversionary thought is in accordance with a previous study of the diversion paradigm in a sample of undergraduate students (Delaney et al., 2010) and with a directed forgetting paradigm employing the list method (Sahakyan et al., 2008) in a sample of younger and older adults. The explanation for this amnesic effect was not addressed in the present study, although context change (i.e., due to the contextual change induced by the diversionary thought, the context of encoding List 1 differed from the context of the memory test) has emerged in the literature as the strongest explanation (Sahakyan and Kelley, 2002; Sahakyan and Delaney, 2005; Delaney et al., 2010). The temporal distance of the diversionary thought (old event: the childhood home *vs* recent event: the last party) does not appear to differentially influence the recall of previously encoded information. To the best of our knowledge, there is no published study on whether the temporal distance created by a diversionary thought influences older adults' forgetting. The result obtained differs from research with undergraduate students that suggests that diversionary thoughts affect the degree of forgetting information (Delaney et al., 2010): when the distance between the present moment and the past remembered event is longer, more forgetting occurs. The analysis of the participants' responses to the post-experiment questionnaire, specifically the responses to the question about the last time they had thought about their childhood home/the last party that they had attended, indicated that the participants in the old event condition had retrieved memories of their childhood home more recently than the participants in the recent event condition had remembered the last party that they had attended. In future studies, the temporal distance of the diversionary thought should be further controlled. The study of these issues will be useful from a practical perspective to promote strategies that enable older adults to better remember important information and more effectively forget irrelevant information, at least immediately after encoding this information. The assessment of executive functions constitutes another limitation of this study, as these functions are strongly related to memory functioning and its decline occurs frequently in older people (e.g., Schaie and Willis, 2009).

The amnesic effect of diversionary thought that was achieved in the present study suggests that this effect is also found in normal aging. Given that remembering a past personal event can have a negative impact on the recall of recently encoded information, training that improves older adults' attentional strategies becomes relevant. This training could help older people remember relevant information and forget unimportant information.

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MINI REVIEW
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Speaking in Alzheimer's disease, is that an early sign? Importance of changes in language abilities in Alzheimer's disease

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It is known that Alzheimer's disease (AD) influences the temporal characteristics of spontaneous speech. These phonetical changes are present even in mild AD. Based on this, the question arises whether an examination based on language analysis could help the early diagnosis of AD and if so, which language and speech characteristics can identify AD in its early stage. The purpose of this article is to summarize the relation between prodromal and manifest AD and language functions and language domains. Based on our research, we are inclined to claim that AD can be more sensitively detected with the help of a linguistic analysis than with other cognitive examinations. The temporal characteristics of spontaneous speech, such as speech tempo, number of pauses in speech, and their length are sensitive detectors of the early stage of the disease, which enables an early simple linguistic screening for AD. However, knowledge about the unique features of the language problems associated with different dementia variants still has to be improved and refined.

Keywords: screening, mild cognitive impairment, Alzheimer's disease, language domain, systematic review

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INTRODUCTION

Despite great efforts concentrated on disease modifying therapies of Alzheimer's disease (AD), halting the degenerative process has not been possible. For this reason, early diagnosis of AD became crucial in the management of the disease. Current pharmacological agents available for AD are more effective in the mild cases, even in the cases of mild cognitive impairments (MCI). It is well-documented that manifest AD patients show markers of language deficit long before their diagnosis is confirmed (Mesulam et al., 2008) and this tendency is especially useful for detecting mild cognitive decline, the prodromal stage of AD (Garrard et al., 2005).

Diagnostic procedures of language functions play a major role in the detection process of the cognitive deficits with different stages. Questions nevertheless remain whether the characterization of the linguistic profiles of MCI/AD cases is useful or not in the detection procedure. The purpose of this review is to summarize the main language deficits in relation to prodromal and manifest AD, focusing on the changes of different language domains (semantic, pragmatic, syntactic, and phonologic ones)

during the course of the disease. Additionally, the relationship between language and other cognitive functions in AD will be discussed.

ALZHEIMER'S DISEASE AND LANGUAGE

Cognitive deficits involve executive function, reasoning, visuoconstructive, and language abilities. Language deficits typically become noticeable from the early stage of the disease (Morris, 1996). Naming disorders, impaired auditory and written comprehension, fluent but empty speech, and semantic paraphasia are typical language deficits in AD, however, repetition abilities and articulation remain relatively intact (Appell et al., 1982; Bayles et al., 1992; Croot et al., 2000). The different stages of the disease exhibit specific patterns of linguistic difficulties in a given domain. The following five domains of language are known: phonetics and phonology, morphology, lexicon and semantics, syntax, and pragmatics. These language domains are affected in different ways in AD (Bayles and Boone, 1982).

In the **Table 1**, we are going to summarize the language function measurements of MCI and different stages in AD. As the disease progresses (from MCI to severe AD), a continuous decline in language can be observed in AD patients (Kempler, 2004).

THE RELATIONSHIP BETWEEN LANGUAGE AND COGNITIVE FUNCTIONS IN ALZHEIMER'S DISEASE

In AD, language and memory functions are closely related since linguistic functioning requires memory functions. Difficulties in productive speech, speech comprehension, and memory functions overlap. Senile changes in language comprehension and expression entail the decline of global speech performance, and a lapse in evocative memory puts constraints on the active vocabulary (Kempler, 2004).

In a summative work, the relationship between simple language measures and cognitive impairment in AD was estimated by the mini-mental state examination (MMSE) and the clinical dementia rating scale (CDR), respectively. Language measures included articulation, fluency (word-finding ability, hypofluency, hyperfluency), semantic fluency, repetition, and confrontational naming. A significant relationship was found between CDR and MMSE scores and all language measures apart from hyperfluency. Impairment in language fluency, animal naming, and confrontational naming are common, especially in the case of impaired cognitive and global performance (Weiner et al., 2008).

It has also been shown that patients with AD show difficulties in performing tasks that tap semantic knowledge, such as naming, verbal fluency, or object recognition. These symptoms occur early and they increase during the course of the illness, suggesting early and progressive impairment of the semantic memory of these patients (Nebes et al., 1989). Briefly, semantic memory can be defined as the capacity to acquire and retain general knowledge about the world, containing basic facts and meanings, as well as words and their meanings. Several approaches have been put forward in order to test semantic memory, such as priming tests, category fluency, and object or picture naming (Hodges, 1994).

Another stream of research aims at the examination of lexical semantic memory (Balthazar et al., 2007). According to these results, the three groups (control, amnestic MCI, mild AD) showed a continuum of decreasing cognitive ability in all cognitive tests. In semantic memory tests, the performance of amnestic MCI patients was similar to that of controls, but showed worse results on verbal fluency task, which involves semantic knowledge, as well as language use, executive function, and short-term memory. Thus, verbal fluency might have been influenced by short-term memory. As the disease progresses, other areas including the temporal cortex are involved, which can explain the difficulties with

TABLE 1 | Alteration in MCI and ad concerning phonetics, phonology, lexicon, semantics, and pragmatics.

Examination methods	Examination results	Sensitivity measures	Reference
Phonetics and phonology			
Temporal analysis of spontaneous speech	Mild AD and CTRL differ in speech tempo and hesitation ratio	No data	Hoffmann et al. (2010)
Temporal analysis of speech, oral reading task	Distinguishes moderate AD and CTRL. Best two parameters: speech tempo and articulation tempo	80%	Martínez-Sánchez et al. (2013)
Spoken task; speech-based detection	Might be a good method for detecting early AD	CTRL and MCI: 80% MCI and AD: 87%	Satt et al. (2014)
Automatic spontaneous speech analysis	Distinguishes between AD and CTRL	No data	López-de-Ipiña et al. (2013)
Lexicon, semantics and pragmatics			
Semantic association test	AD performs significantly worse than CTRL	No data	Visch-Brink et al. (2004)
Semantic verbal fluency and phonological verbal fluency	Good tool for diagnosis of early AD	No data	Laws et al. (2010)
Picture naming, semantic probes, lexical decision and priming, Stroop-picture naming	AD group was impaired in semantic tasks	No data	Duong et al. (2006)
Verbal task	AD group produces shorter texts, less relevant information and multiple error types than CTRL	No data	Taler and Phillips (2008)

AD, Alzheimer's disease; MCI, mild cognitive impairment; CTRL, healthy controls.

semantic knowledge in mild AD. It has been shown that amnestic MCI impairs episodic memory while the lexical semantic system is spared, which can be affected in the early phase of AD.

In summary, deficits in language and memory functions, especially in semantic memory are commonly found in patients with AD, even in the early phase. Therefore, the need can arise for developing a purely language-based screening test, which can serve as an early diagnostic tool for MCI.

NEURAL BASES OF LANGUAGE DEFICITS IN ALZHEIMER'S DISEASE

Considering the cognitive impairments in AD, the neural basis of episodic memory has been primarily investigated by the anatomical and functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), or positron emission tomography (PET). So far, only a limited number of publications are available, which focus on the detection of organic or functional changes in the central nervous system underlying language impairments. For example, a recent investigation of healthy subjects and individuals with amnestic mild cognitive impairment (aMCI) demonstrated a difference in the neuroanatomical bases of episodic and semantic performance (Hirni et al., 2013). Specifically, region of interest (ROI) analyses showed that episodic memory performance was associated with the bilateral entorhinal cortex/hippocampus (ERC/HP) head, whereas semantic memory performance was associated with left medial perirhinal cortex (mPRC) and bilateral ERC/HP head integrity suggesting that mPRC damage in very early AD may be detectable with common clinical tests of semantic memory if episodic memory performance is controlled (Hirni et al., 2013).

In another study, a 2-back versus 1-back letter recognition task was performed by MCI and AD patients, using DTI and fMRI. Significant hypoactivation was found in posterior brain areas and relative hyperactivation in anterior brain areas during working memory in AD/MCI subjects compared to controls. In MCI/AD subjects, impairments of structural fiber tract integrity co-occur with breakdown of posterior and relatively preserved anterior cortical activation during working memory performance (Teipel et al., 2014).

Posterior corpus callosum connects superior parietal, posterior temporal, and occipital cortical areas (De Lacoste et al., 1985), which include key nodes of working memory activation. The superior longitudinal fasciculus forms a large arc superior and lateral to the putamen connecting all four cerebral lobes, which has a main role in language processing in the human brain (Bernal and Altman, 2010; Axer et al., 2013). This area is known to be impaired in MCI and mild AD (Liu et al., 2011; Zhang et al., 2013) and is a possible reason for functional uncoupling of prefrontal and posterior brain areas during verbal working memory performance (Teipel et al., 2014).

LANGUAGE FUNCTIONS DURING THE COURSE OF ALZHEIMER'S DISEASE

The impairment of the language functions in the course of AD may be characteristic not only for the given stage of the disease but also for its prodroma, MCI. During the total course of the disease, language seems to be impaired disproportionally, meaning that the semantic and pragmatic language systems are more impaired than syntax (Bayles and Boone, 1982). Impairments in the lexical, semantic, and pragmatic language functions are typically present in mild AD since they depend on cognition to a greater extent (Taler and Phillips, 2008; Tsantali et al., 2013). Articulatory and syntactic domains of language production remain intact until late stages of the disease (Croot et al., 2000).

In the following sections, relevant studies will be discussed and summarized in order to investigate language functioning during the course of AD, considering the most extensively researched language domains (**Table 2**).

Phonetics and Phonology in Alzheimer's Disease

Temporal parameters of speech can be investigated in the language domains phonetics and phonology, more precisely, in spontaneous speech (Hoffmann et al., 2010; López-de-Ipiña et al., 2013), in a reading aloud task (Martínez-Sánchez et al., 2013), and in spoken tasks (Satt et al., 2014).

In the MCI phase, the most characteristic linguistic changes are longer hesitations and a lower speech rate in spontaneous speech (Hoffmann et al., 2010; Roark et al., 2011; Jarrold et al., 2014; Satt et al., 2014). The manually extracted acoustic features of spontaneous speech and an automatizing biomarker extraction process using automatic speech recognition (ASR) have been recently compared in MCI patients and control subjects (Tóth et al., 2015). The classification results provided by ASR-based feature extraction were just slightly worse than those of the manual method (Tóth et al., 2015).

The temporal parameters of spontaneous speech have also been investigated in mild AD and control subjects (Hoffmann et al., 2010). This study aimed to identify a speech parameter that might distinguish mild AD patients from normal individuals. The following aspects of spontaneous speech were included in the analysis: articulation rate, speech tempo, hesitation ratio, and grammatical error ratio. Results showed that articulation rate in mild and severe AD patients was significantly different from normal controls; furthermore, a difference among mild, moderate, and severe AD patients was also reported. Significant differences in speech tempo and hesitation ratio were found between all experimental groups, apart from moderate and severe AD patients, who performed similarly on both tasks. Grammatical error analysis showed significant difference between moderate and severe AD groups; however, this was not found when comparing normal subjects and mild AD groups (Hoffmann et al., 2010).

In another study, an automatic spontaneous speech analysis was also carried out to identify mild AD. It was suggested that shorter recording times reflect that for AD patients, speech requires more efforts than for healthy individuals: patients speak more slowly with longer pauses, as well as they spend more time to find the correct word, which in turn leads to speech disfluency or break messages (López-de-Ipiña et al., 2013).

A similar research studied the temporal organization of speech in AD patients and matched healthy controls with an oral reading

TABLE 2 | Language functions in mild cognitive impairment and in the different stages of Alzheimer's disease.

Language characteristic changes		MCI	Mild AD	Moderate AD	Severe AD	Reference
Phonetics-phonology						
Temporal changes in spontaneous speech (increasing hesitation number and time)		+	+	++	+++	Forbes and Venneri (2005); Hoffmann et al. (2010); Roark et al. (2011); Meilán et al. (2012); Satt et al. (2014); Jarrold et al. (2014); Laske et al. (2015)
Phonemic paraphasia		+	+	++	+++	Croot et al. (2000); Forbes et al. (2002); Hoffmann et al. (2010); Wutzler et al. (2013); Roark et al. (2011); Satt et al. (2014); Jarrold et al. (2014)
Lexical-semantics						
Word-finding and word retrieval difficulties		+	+	++	+++	Smith et al. (1989); Bayles (1993); Light (1993); Kempler and Zelinski (1994); Kempler et al. (2001); Garrard et al. (2005); Taler and Phillips (2008); Dos Santos et al. (2011); Cardoso et al. (2014); Fraser et al. (2014); Laske et al. (2015); Garrard et al. (2014)
Verbal fluency difficulties	Phonemic (letter)	+	+	++	+++	Barth et al. (2005); Juncos-Rabadán et al. (2010); Hoffmann et al. (2010); Dos Santos et al. (2011); Roark et al. (2011); Satt et al. (2014); Jarrold et al. (2014)
	Semantic	+	+	++	+++	
Semantic paraphasia		?	+	++	+++	Juncos-Rabadán et al. (2010); Hoffmann et al. (2010); Roark et al. (2011); Satt et al. (2014); Jarrold et al. (2014)
SYNTAX						
Reduced syntactic complexity		–	–	+	+++	Caramelli et al. (1998); Small et al. (1997); Kempler (1995); Bickel et al. (2000); Ullman (2001); Juncos-Rabadán et al. (2010)
Agrammatisms		–	–	–	+++	Small et al. (1997); Kempler (1995); Ullman (2001)
DISCOURSE-PRAGMATICS						
Reduction in productive and receptive discourse-level processing		–/+	+	++	+++	Hodges et al. (1992); Ripich (1994); Taler and Phillips (2008); Weiner et al. (2008); Hoffmann et al. (2010); Juncos-Rabadán et al. (2010); Rapp and Wild (2011); Tsantali et al. (2013); Cardoso et al. (2014)

AD, Alzheimer's disease; MCI, mild cognitive impairment.
The scale of MMSE scores is as follows: MCI: 28–26 points (Roalf et al., 2013), mild AD: 25–20 points, moderate AD: 19–10 points, and severe AD: 9–0 points (Vertesi et al., 2001).
+, degree of involvement; –, intact; ?, no data.

task. The following indices were analyzed: total duration of the reading task, number of pauses, pause proportion, phonation time, phonation – time ratio, speech rate, and articulation rate. The AD group showed impairment in all of these variables. Reduced speech and articulation rates, low effectiveness of phonation time, as well as increased number and proportion of pauses characterized their reading. The two temporal parameters with the greatest discriminatory capacity were speech rate and articulation rate. In sum, signal processing algorithms applied to reading fluency recordings were capable of differentiating between AD patients and controls with an accuracy of 80% based on speech rate. Thus, analyzing temporal parameters for reading fluency, especially speech and articulation rates, allowed to distinguish between asymptomatic subjects and patients in mild AD (Martínez-Sánchez et al., 2013).

Although examining the temporal parameters of spontaneous speech, it is not clear which variables are capable of separating the mild AD group from the control group. Some researchers divided the mild AD group from the control group based on the articulation rate, speech tempo, and hesitation ratio variables (Hoffmann et al., 2010), whereas others suggested that speech rate and articulation rate are the best discriminating variables (Martínez-Sánchez et al., 2013). Furthermore, some researchers emphasize the importance of break analysis as well (López-de-Ipiña et al., 2013). However, there is an agreement that the temporal analysis of spontaneous speech is proven to be an effective method for spotting mild AD.

In moderate or severe AD, there are more and more serious temporal changes in spontaneous speech: hesitation number and time increase, compared to mild AD, and the mental lexicon is even more difficult to access (Hoffmann et al., 2010).

Lexical, Semantic, and Pragmatic Domains of Language in Alzheimer's Disease

Mild cognitive impairment patients usually have trouble with finding the right word (Fraser et al., 2014; Garrard et al., 2014). As regards semantics and syntax, both seem to be impaired since fluency tasks and naming tasks show deficits; moreover, comprehension of sentences and texts and production of narrative speech are also impaired, concerning the semantic content and syntactic structures of speech (Juncos-Rabadán et al., 2010).

Alzheimer's disease patients lack the distinctive semantic attributes of concepts: there is strong evidence that dysfunction in linguistic tasks is caused by the general cognitive impairment in AD (Feinberg and Farah, 1997). The most common and obvious language errors made by AD patients are semantic errors (Croot et al., 2000), namely that they use superordinate category names instead of the target name (Saito and Takeda, 2001) or circumlocutory speech with progressively impaired naming (Emery, 2000).

The semantic association test (SAT) is a tool for detecting disorders in verbal and visual semantic processing (Visch-Brink and Denes, 1993). In general, AD patients had significantly lower scores on SAT than controls. However, their data expose an incoherent relation between naming and semantic processing in AD. In contrast to semantic processing, the performance of

AD patients on naming fell within the normal range, implying that naming is independent of semantic processing in AD (Visch-Brink et al., 2004).

Alzheimer's disease patients typically have difficulties in tasks of confrontational naming and verbal fluency (Appell et al., 1982; Bayles et al., 1987). Semantic verbal fluency and phonological verbal fluency tests are widely used in diagnosis of AD and they are reliable indicators of language deterioration in the early detection of AD (Laws et al., 2010). Difficulties in word finding are one of the earliest manifestations of language breakdown in AD. This pattern of impairment has been implicated as the loss of semantic knowledge in AD (Hodges et al., 1992). Results from language tests and priming experiments clearly suggest altered intentional and automatic semantic processes in AD. However, the order in which these processes are impaired during the course of the disease is unclear (Duong et al., 2006).

Lexico-semantic impairments in AD have been attributed to abnormalities in intentional and automatic access to semantic memory. In a study, MCI, pre-AD, and normal elderly people were tested with intentional access tasks (picture naming and semantic probes), automatic access tasks (lexical decision and priming), and executive function tasks (Stroop and Stroop-picture naming). Results indicated that the MCI group was only impaired in tasks of intentional access relative to the AD group, which showed impairment in all tasks. Since most MCI subjects eventually develop AD, the results suggest that the intentional access to semantic memory is impaired earlier compared to the automatic access. The AD individuals performed significantly different from normal controls in all four semantic tasks (Duong et al., 2006). AD subjects demonstrated slowing in lexical decision as well as increase in semantic priming, termed hyperpriming (Giffard et al., 2001, 2002), which speaks for abnormal automatic semantic processing. Abnormal performance has also been found in picture naming and semantic probe questions which require effortful semantic processing and search. The results confirmed the observation that subtle cognitive impairments, such as language impairment, may co-occur with the readily observed memory impairments (Petersen et al., 1999, 2001; Ritchie et al., 2001).

Alterations in productive and receptive discourse-level processing have also been reported in MCI and mild AD. AD individuals generally produce shorter texts than the normal controls with less relevant information and multiple error types (incoherent/indefinite phrases, semantic and graphemic paraphasia, and inability to abstract) and describe all pictorial themes (Taler and Phillips, 2008).

To sum up, we can say that the performance of AD patients is different compared to the control group in most of the semantic tasks. Changes in semantic processing (Petersen et al., 1999, 2001; Ritchie et al., 2001; Duong et al., 2006) trigger semantic errors in AD patients (Croot et al., 2000). Furthermore, impaired naming (Emery, 2000) and picture naming (Petersen et al., 1999, 2001; Ritchie et al., 2001), word finding difficulties, and abnormal verbal fluency are also present in this group (Appell et al., 1982; Bayles et al., 1987). Slow lexical decision could be one of the reasons behind all of these (Giffard et al., 2001, 2002). However, it should be noted that although lexico-semantic changes in AD have been intensively studied, research on pragmatics has rarely been carried out among AD patients, thus it constitutes a potential field for future investigations.

CONCLUSION

On the basis of the existing research findings, we can state that the language deficit in AD is present in the early stage of the disease; therefore, the objective measures of the different language domains are very important in the recognition of these patients. However, up to now, very few linguistic methods have been published, which are suitable for the early diagnosis of AD.

The disproportional impairments of language functions in the course of the disease have been proven by almost cohort studies. Large scale prospective longitudinal studies would be more beneficial; however, they have been also missing. Additionally, more extensive use of functional neuroimaging techniques based on linguistic tasks in MCI or mild AD could lead to a more informed picture of the neural bases of language functions in the different stages of the disease.

In the future, additional work needs to be done to validate new methods across different settings (such as population-based, primary care, and memory clinics), age, and ethnic groups. Since the earliest measurable language domain is the temporal parameter of speech, the computerized analysis of spontaneous speech developed recently may be a promising approach in the early detection of AD. The combined use of the measurement of linguistic parameters and telemedicine technologies might permit the screening of MCI or mild AD by an interactive test using a software package or mobile application. Having an accurate method to assess for dementia and predict risk in routine clinical care will aid decision-making and can ultimately lead to disease prevention.

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frontiers in Aging Neuroscience

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The neural mechanisms underlying the aging-related enhancement of positive affects: electrophysiological evidences

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Background: Previous studies reported that old adults, relative to young adults, showed improvement of emotional stability and increased experiences of positive affects.

Methods: In order to better understand the neural underpinnings behind the aging-related enhancement of positive affects, it is necessary to investigate whether old and young adults differ in the threshold of eliciting positive or negative emotional reactions. However, no studies have examined emotional reaction differences between old and young adults by manipulating the intensity of emotional stimuli to date. To clarify this issue, the present study examined the impact of aging on the brain's susceptibility to affective pictures of varying emotional intensities. We recorded event-related potentials (ERP) for highly negative (HN), mildly negative (MN) and neutral pictures in the negative experimental block; and for highly positive (HP), mildly positive (MP) and neutral pictures in the positive experimental block, when young and old adults were required to count the number of pictures, irrespective of the emotionality of the pictures.

Results: Event-related potentials results showed that LPP (late positive potentials) amplitudes were larger for HN and MN stimuli compared to neutral stimuli in young adults, but not in old adults. By contrast, old adults displayed larger LPP amplitudes for HP and MP relative to neutral stimuli, while these effects were absent for young adults. In addition, old adults reported more frequent perception of positive stimuli and less frequent perception of negative stimuli than young adults. The post-experiment stimulus assessment showed more positive ratings of Neutral and MP stimuli, and reduced arousal ratings of HN stimuli in old compared to young adults.

Conclusion: These results suggest that old adults are more resistant to the impact of negative stimuli, while they are equipped with enhanced attentional bias for positive stimuli. The implications of these results to the aging-related enhancement of positive affects were discussed.

Keywords: aging, event-related potentials, positive affects, late positive potentials, attention

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Introduction

Although human aging is associated with reductions of physical and cognitive abilities, many studies indicate that emotional stability and positive affects may enhance with normal aging (Mroczek and Kolarz, 1998; Ehrlich and Isaacowitz, 2002; Clark and Oswald, 2007). In an early study, Mroczek and Kolarz (1998) observed that old adults tend to report less negative experience and more positive experience than young adults. Consistent with this aging-related enhancement of emotional stability, a number of studies have demonstrated that relative to young adults, old adults showed preferential processing of positive information over negative information (Williams et al., 2006; Wood and Kisley, 2006; Kisley et al., 2007; Leclerc and Kensinger, 2008a; Feng et al., 2011), which is known as the aging-related positivity effect. Allard and Isaacowitz (2008) observed that old adults fixated more toward positive and neutral than negative pictures in both full and divided attention conditions. By recording eyeblink startle responses, Feng et al. (2011) reported that old adults showed potentiated responses when viewing positive pictures in comparison to negative pictures, whereas this was not the case for young adults. Socioemotional selectivity theory (SST) provides a framework for understanding the aging-related enhancement of positive affects. This theory states that motivation and goal preferences are influenced by time perspective (Carstensen et al., 1999). Young adults perceive their time remaining in life to be expansive and are more motivated to acquire knowledge whereas old adults perceive their time left in life as limited and would prioritize present-oriented goals of emotional meaning (Carstensen et al., 1999). This motivational shift leads to that old adults focus more attention on positive aspect of life.

A number of studies have investigated neural underpinnings of the aging-related enhancement of positive affects (Williams et al., 2006; Wood and Kisley, 2006; Kisley et al., 2007; Leclerc and Kensinger, 2008a). Using both event-related potential (ERP) and functional MRI methods, Williams et al. (2006) found that aging was associated with enhanced medial prefrontal activation for fearful faces and smaller activation for happy faces. The enhanced prefrontal control of negative and smaller control of positive information with aging has been considered as an important explanation for this phenomenon (Williams et al., 2006). In addition, several studies reported that the aging-related enhancement of positive affects is driven primarily by decreased neural responding to negative materials (Wood and Kisley, 2006; Kisley et al., 2007). For example, using an emotional categorization task and ERP technique, Kisley et al. (2007) observed age-related reductions in neural reactivity to negative pictures, but little age-related changes in neural reactivity to positive pictures. However, other studies demonstrated that this phenomenon is driven primarily by increased brain reactions to positive materials (Mather et al., 2004; Leclerc and Kensinger, 2008a). For example, by requiring subjects to identify the uses of emotional objects, Leclerc and Kensinger (2008a) observed greater activations of ventromedial prefrontal cortex for positive than for negative pictures in old adults, whereas young adults showed enhanced activations for negative than for positive pictures in this region.

Thus, there exist disagreements concerning the neural mechanisms behind the aging-related enhancement of positive affects. Though Williams et al. (2006) suggest that the aging-related shift in prefrontal control of negative and positive stimuli contributes to this phenomenon, this inference was based on a face perception task, instead of a direct emotional control task. Of particular importance, it needs to be elucidated whether this phenomenon is driven solely by decreased brain reactions to negative materials or by enhanced reactions to positive materials, or by both. It is worth noting that most of the prior studies which addressed neural mechanisms of this phenomenon required subjects to assess the emotionality of the stimuli explicitly (Mather et al., 2004; Williams et al., 2006; Wood and Kisley, 2006; Kisley et al., 2007; Leclerc and Kensinger, 2008a). It has been indicated that emotional effects are susceptible to the contamination of the explicit categorization of emotional stimuli, which is known as the "relevance-for-task effect" that is most pronounced in ERP experiment (Carretié et al., 1996, 2001). Thus, it is necessary to design a covert emotional task to control this confound. On the other hand, in order to obtain a clean emotional effect, it is necessary to set non-emotional, neutral stimuli as a baseline for positive or negative stimuli, and then to compute the emotion effect based on the emotional-neutral differences in dependent variables (Meng et al., 2009; Yuan et al., 2009), rather than simply comparing positive with negative stimuli.

Furthermore, in order to better understand the neural underpinnings behind the aging-related enhancement of positive affects, it is necessary to investigate whether old and young adults differ in the threshold of eliciting positive or negative emotional reactions. Specifically, because it is well established that aging is linked with better emotional stability and increased positive affects, it is possible that old adults are reactive to positive stimuli of low emotional intensity, which may not be the case for young adults. Similarly, given the robustness of this aging-related phenomenon, old adults are also likely to elicit emotional reactions to negative stimuli at a higher threshold than young adults. However, no studies have examined emotional reaction differences between old and young adults by manipulating the intensity of emotional stimuli to date. In fact, a great number of prior studies confirmed that the intensity of emotional stimuli is important (Leppänen et al., 2007; Yuan et al., 2007; Meng et al., 2009; Schaefer et al., 2009), and emotions of diverse intensities modulate cognitive activities differently (Yuan et al., 2008, 2012; Schaefer et al., 2009, 2011). Without manipulation of the emotional intensity of positive and negative stimuli, it is difficult to reveal the difference in the threshold of emotion elicitation across age groups.

In addition, a number of studies have indicated that the impact of aging on processing of emotional stimuli is clearly observed in controlled processing tasks which involve prefrontal cortex activity (Carstensen et al., 1999; Leclerc and Kensinger, 2008a); while this impact is not observed in tasks involving automatic processing (Hahn et al., 2006; Mather and Knight, 2006; Leclerc and Kensinger, 2008b; Mickley Steinmetz et al., 2010). For

example, using eye-tracking method, Rosler et al. (2005) reported that when a negative–neutral picture pair was presented, young adults maintained attention longer toward negative pictures than old adults did, but young and old adults showed similar initial attentional orienting for the negative pictures. Using a spatial-cueing task, Brassen et al. (2011) reported that relative to young adults, old adults showed increased distractibility by happy faces in the high attention to faces condition. However, this age difference vanished when attention was low to faces (Brassen et al., 2011). Although these studies imply that the impact of aging on emotional processing entails the access of controlled processing resources (Leclerc and Kensinger, 2008a; Mickley Steinmetz et al., 2010; Sasse et al., 2014), how emotion-related aging effect varies with the information processing stages has yet to be directly investigated.

Based on the above considerations, the present study aimed to address the impact of aging on automatic and controlled processing of positive and negative stimuli of varying emotional intensity, by using ERP measures and a block-design covert-emotional task. We used ERP technique as it is helpful in depicting the timing features, specifically, the automatic and controlled processing of emotional stimuli and their modulation by aging. Previous studies used two ERP components, P1 and late positive potential (LPP), to reflect automatic and controlled processing, respectively (Wood and Kisley, 2006; Kisley et al., 2007; Olofsson et al., 2008; Langeslag and Van Strien, 2010). P1 component is an early component peaking about 100 ms post stimulus and has been accepted to reflect exogenous, automatic sensory processing (Scott et al., 2009; Dan and Raz, 2012). P1 amplitudes are thought to be sensitive to attention allocation (Luck et al., 1994; Smith et al., 2003; Brown et al., 2010), and be heightened for emotional stimuli compared to neutral stimuli (Scott et al., 2009; Dan and Raz, 2012). By contrast, LPP, which is also named late positive component (LPC) by some researchers (Ashley et al., 2004; Langeslag et al., 2007), starts around 400 ms and lasts for 700 ms. LPP reflects consciously controlled processing that involves continued voluntary attention toward emotional stimuli (Hajcak and Dennis, 2009; Langeslag and Van Strien, 2010). The LPP amplitudes increased with the enhancement of experienced emotion, and decreased with the reduction of experienced emotion (Flaisch et al., 2008; MacNamara et al., 2011). Based on previous studies (Carstensen et al., 1999; Hahn et al., 2006; Mather and Knight, 2006; Leclerc and Kensinger, 2008a,b; Mickley Steinmetz et al., 2010), we predict that the impact of aging on brain processing of emotional stimuli may occur at voluntary attention stage, instead of early automatic attention stage. Specifically, young and old adults may display similar emotional reactivity to emotional pictures in early P1 component whereas the two groups may display different emotional reactivity to pictures in LPP component.

In addition, considerable studies with young adults indicate that LPP elicited by negative pictures are largest over the parietal scalp (Cuthbert et al., 2000; Hajcak and Olvet, 2008; Yuan et al., 2014a,b). Based on these evidences, if old adults relative to young adults show decreased negative emotional reactivity, it is likely to observe decreased LPP amplitudes for negative pictures at parietal scalp, in old compared to young adults. On the other hand, functional MRI studies have indicated that the processing bias of old adults for positive stimuli is mainly manifested by the greater neural activity for positive relative to negative stimuli in prefrontal cortical regions (e.g., ventromedial or dorsolateral PFC; Leclerc and Kensinger, 2008a; Ritchey et al., 2011). However, the covert emotional task is associated with similar late potentials for positive and neutral stimuli in young adults (Yuan et al., 2007, 2009). Based on these evidences, we hypothesize to observe enhanced LPP amplitudes for positive compared to neutral pictures at prefrontal scalp, in old adults but not in young adults.

On the other hand, previous studies often used a random design, which presented positive, negative and neutral stimuli in a single block, with their order fully randomized (Wood and Kisley, 2006; Kisley et al., 2007). Though these studies observed clear emotion effects in electrophysiological measures, they observed no emotional effect in behavioral measures (Wood and Kisley, 2006; Kisley et al., 2007). A possible reason is that presenting positive to negative (or negative to positive) stimuli across trials may produce inter-trial emotion offset, which prevents the generation of a robust emotion induction effect in behavioral assessment. However, it is important to assess emotion impact from behavioral measures, not only for confirming whether a given type of emotional stimuli effectively elicit the target emotion, but also for verifying what neurophysiologic results truly reflect. For these considerations, the current study used a block design (Rowe et al., 2007; Yuan et al., 2012), with one block presenting highly positive (HP), mildly positive (MP) and neutral pictures while the other block presenting highly negative (HN), mildly negative (MN) and neutral pictures. A neutral baseline condition was used in either block, to isolate the emotional effect for each condition. To investigate the behavioral index of emotion impact and its relation with aging, subjects were asked to report the perceived frequency and the category of emotional images for each block, according to subjective impressions. We used this procedure, rather than direct mood rating, to avoid a potential floor effect in mood data because emotional stimuli were intermixed with neutral stimuli in either block. If old adults truly differ from young adults in susceptibility to positive or negative stimuli, the perceived frequency should be different across age groups. This method has been verified effective in reflecting group differences in susceptibility to emotional stimuli in our prior study (Yuan et al., 2009).

Lastly, in order to avoid cultural bias when International Affective Picture System (IAPS) was used directly in Chinese subjects (Huang and Luo, 2004), the pictures used to elicit emotional responses in the present study were selected from the native Chinese Affective Picture System (CAPS), which was established in a similar way to IAPS (Bai et al., 2005). According to the widely accepted dimensional theory of emotion, the affective significance of a stimulus is organized along the two primary dimensions: valence and arousal (Lang et al., 1997; Bradley et al., 2001). Intense emotional stimuli are normally accompanied by higher arousal in comparison with mildly emotional stimuli, irrespective of whether the stimuli

are positive or negative (Bradley et al., 1990; Lang et al., 1997; Cuthbert et al., 2000; Keil et al., 2002; Kuppens et al., 2013). Thus, we predict that HP pictures would be rated more positive and more arousing than MP pictures; and HN pictures be rated more negative and more arousing than MN pictures.

Materials and Methods

Subjects

As paid volunteers, 17 young adults (age: 18–22; 8 females) and 17 old adults (age: 60–74; 9 females) in local community were randomly sampled for the experiment. The gender composition was not significantly different across the two samples [χ^2 (1) = 0.118, $p = 0.73$]. All the subjects were right-handed and had no self-reported visual problems. As a final check of visual function, all the subjects read textual instructions on a computer screen at a distance of 2.5 m easily. In addition, both young and old adults were healthy, reporting no current symptoms and no history of anxious or depressive disorders. No subjects were taking medication that would affect the central nervous system. Each participant signed an informed consent form prior to the experiment. The experimental procedure was in accordance with the ethical principles of the 1964 Declaration of Helsinki (World Medical Organization [WHO], 1996). Prior to the experiment, the life satisfaction (LS) was assessed by the subjects answering "how is your life recently?" ranging from 1: very stressful; 3: ordinary to 5: very good. The scores of young adults were not significantly different from 3 [$t(16) = 1.098$, $p = 0.289$], while old adults' rating was higher than 3 [$t(16) = 4.243$, $p = 0.001$]. The LS was higher for old (4.055) relative to young adults [3.294; $t(32) = -2.088$, $p = 0.045$).

Stimulus Materials

The present study included two experimental blocks. Each block consisted of 168 pictures (grouped into three conditions). In the positive block, 168 pictures were grouped as HP, MP, or neutral. Like many other studies using IAPS, the pictures used for this study covered a variety of contents (Cuthbert et al., 2000; Smith et al., 2003), such as highly pleasant, mildly pleasant, or neutral animals (e.g., puppies, pandas, or wolfs), natural scenes (e.g., landscapes, seashores, or mountains) and human activity (e.g., cheers, sports, conversation). In the negative block, 168 pictures were grouped as HN, MN, or neutral; such as HN, MN, or neutral animals (e.g., snakes, bugs, or eagles), natural scenes (e.g., fire disaster, flood, clouds) and human activity (e.g., homicide, violence, or sports). All the 336 pictures were selected from the CAPS. In the positive block, the three sets of pictures differed significantly from one another in both valence [$F(2,165) = 286.14$, $p < 0.001$] and arousal [$F(2,165) = 290.54$, $p < 0.001$]. HP pictures were rated more positive than were MP pictures [$F(1,110) = 86.62$, $p < 0.001$] which, in turn, were rated positive compared with the Neutral pictures [$F(1,110) = 121.63$, $p < 0.001$]. Also, HP pictures were rated more arousing relative to MP pictures [$F(1,110) = 98.76$, $p < 0.001$] which, again, were rated more arousing than were Neutral stimuli [$F(1,110) = 145.49$, $p < 0.001$]. In the negative block, the three sets of pictures differed significantly from one another in valence [$F(2,165) = 1348.33$, $p < 0.001$] and arousal [$F(2,165) = 615.69$, $p < 0.001$]. HN pictures were rated more negative than were MN pictures [$F(1,110) = 293.65$, $p < 0.001$] which, in turn, were rated negative compared with the Neutral pictures [$F(1,110) = 1337.01$, $p < 0.001$]. Also, HN pictures were rated more arousing relative to MN pictures [$F(1,110) = 273.37$, $p < 0.001$] which, again, were rated more arousing than were Neutral pictures [$F(1,110) = 379.2$, $p < 0.001$, see **Figure 1**]. All the pictures were identical in size and resolution (15 cm × 10 cm, 100 pixels per inch). In addition, the luminance level of the pictures was tested prior to experiment, and the luminance level and spatial frequency were matched across the three conditions in each block. The contrast of the monitor was set to a constant value across subjects.

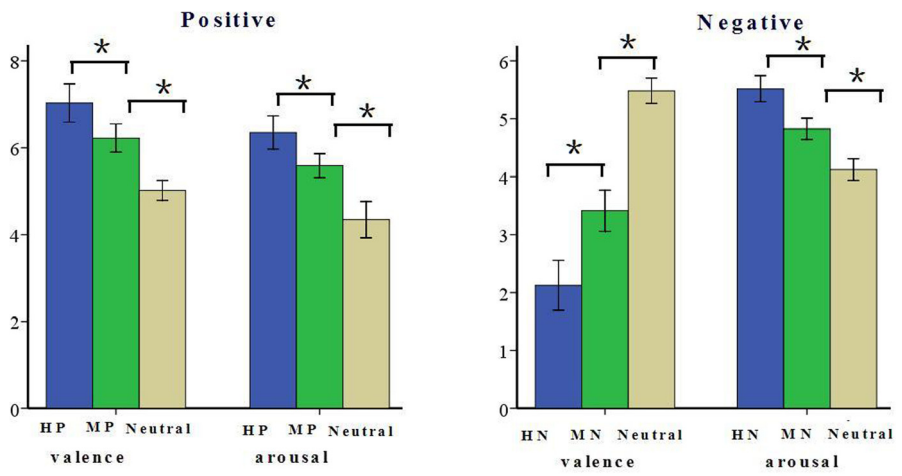

FIGURE 1 | Schematic illustration of the means and SD of valence and arousal assessments based on Normative Ratings (Bai et al., 2005). *$p < 0.05$.

Behavioral Procedures

Subjects were seated in a quiet room at approximately 150 cm from a computer screen with the horizontal and vertical visual angles below 6°. Subjects were required to count the number of pictures. Each trial was initiated by a fixation cross for 1000 ms. The offset of the fixation was followed by the presentation of picture stimulus for 1000 ms. The inter-trial interval ranged randomly between 800 and 1000 ms. Each of the 336 pictures was just presented for once during the experiment. Between the two experimental blocks, 3 min of rest was used to prevent fatigue. The present study used E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) to control the presentation and timing of all stimuli. Each picture was displayed in color and occupied the entire screen of a 19-in. (48.26 cm) monitor at a 60-Hz refresh rate with a resolution of 1024 × 768 pixels of the screen. Each subject participated in both experimental blocks, with order of the blocks counterbalanced across subjects. In the rest period, subjects were asked to report the perceived frequency by percentage and the category of emotional images in negative and positive blocks, respectively, according to their subjective impressions. After the EEG recording, subjects were asked to rate the valence and arousal of the pictures using the Self-Assessment Manikin procedure (SAM; Lang et al., 1997). Using a self-report nine-point rating scale, subjects were required to rate the emotion valence (ranging from 1 = "very negative" to 9 = "very positive") and arousal (ranging from 1 = "very calm" to 9 = "very excited") they felt for each image by pressing corresponding number keys in the keyboard. The sequence of the two ratings was counterbalanced across subjects.

ERP Recording and Analysis

The EEG was collected on 64 scalp sites using tin electrodes mounted in an elastic cap (Brain Products), with the references on the left and right mastoids (average mastoid reference, Luck, 2005) and a ground electrode on the medial frontal aspect. Vertical electrooculograms (EOGs) were recorded above and below the left eye. Horizontal EOG was recorded from the left versus right orbital rim. EEG and EOG activity was amplified at a bandpass of DC∼100 Hz and digitized with a sampling rate of 500 Hz. The EEG was filtered between 0.01 and 16 Hz. EEG recording did not start until all electrode impedances were kept below 5 kΩ. ERP averages were computed off-line; Trials with EOG artifacts (mean EOG voltage exceeding ±80 μV) and those contaminated with artifacts due to amplifier clipping, or peak-to-peak deflection exceeding ±80 μV were excluded from averaging.

EEG activity in each condition was averaged separately. ERP waveforms were time-locked to the onset of stimuli and the averaging epoch was 1200 ms, including a 200 ms pre-stimulus baseline. We selected the following nine electrode sites for statistical analysis of LPP amplitudes (400–1000 ms): FPz, FP1, FP2 (three prefrontal sites), Cz, C3, C4 (three central sites), Pz, P3, and P4 (three parietal sites). A repeated measures ANOVA of mean LPP amplitudes was conducted with the following repeated factors: emotion intensity (three levels: HN, MN, and neutral for negative block; HP, MP, and neutral for positive block), frontality (three levels: prefrontal, central, and parietal), and laterality (three levels: left, midline, and right) in negative and positive block, separately. Aging was used as a between-subjects factor. In order to explore the timing features of LPP modulation in old and young samples, the LPP waveform was quantified by mean amplitude measures in three time windows: 400–600 ms, 600–800 ms, 800–1000 ms, as recommended by prior studies (Hajcak and Nieuwenhuis, 2006; Foti and Hajcak, 2008). On the other hand, the mean amplitudes of occipital P1 (70–130 ms) were analyzed at O1, Oz, and O2 (three occipital sites), to explore the effects of aging on early visual processing. A repeated measures ANOVA was performed with emotion, block, electrode and aging as factors. The degrees of freedom of the *F*-ratio were corrected according to the Greenhouse–Geisser method in all these analyses. The *post hoc* pairwise comparisons were conducted using Bonferroni–Holm correction method if a significant main or interaction effect was detected.

Results

Cognitive Performances during the Counting Task

In the negative block, 15 old adults and 16 young adults accurately reported the number of pictures. In the positive block, 14 old adults and 15 young adults accurately reported the number of pictures. The proportion of subjects who accurately reported the number of pictures was not significantly different between the two samples in both negative [$\chi 2\ (1) = 0.366$, $p = 0.545$] and positive [$\chi 2\ (1) = 0.234$, $p = 0.628$] blocks. These results suggest that the two age groups did not differ in cognitive performances during the counting task.

Emotion Assessment

A repeated measures ANOVA of arousal and valence ratings was conducted with the following factors: emotion intensity (three levels: HN, MN, and neutral for the negative block; HP, MP, and neutral for the positive block), and age (young, old). The results in the negative block showed a significant main effect of emotion intensity in valence rating [$F(2,64) = 104.949$, $p < 0.001$]. HN pictures were rated more negative than were MN pictures [$F(1,32) = 91.824$, $p < 0.001$] which, in turn, were rated negative compared with the Neutral pictures [$F(1,32) = 79.229$, $p < 0.001$]. Also, there was a significant main effect of emotion intensity in arousal rating [$F(2,64) = 158.217$, $p < 0.001$]. HN pictures were rated more arousing relative to MN pictures [$F(1,32) = 217.687$, $p < 0.001$] which, again, were rated more arousing than were Neutral stimuli [$F(1,32) = 80.864$, $p < 0.001$]. In addition, there was a significant interaction between emotion intensity and aging in arousal rating [$F(2,64) = 14.087$, $p < 0.001$]. The breakdown of the interaction shows that the arousal rating was higher in young than in old adults in HN [$F(1,32) = 12.748$, $p < 0.01$], but not in Neutral [$F(1,32) = 2.161$, $p = 0.151$] and MN [$F(1,32) = 2.191$, $p = 0.149$] pictures (see **Figure 2**).

The results in the positive block showed a significant main effect of emotion intensity [$F(2,64) = 6.657$, $p < 0.01$] and a significant interaction between emotion intensity and aging

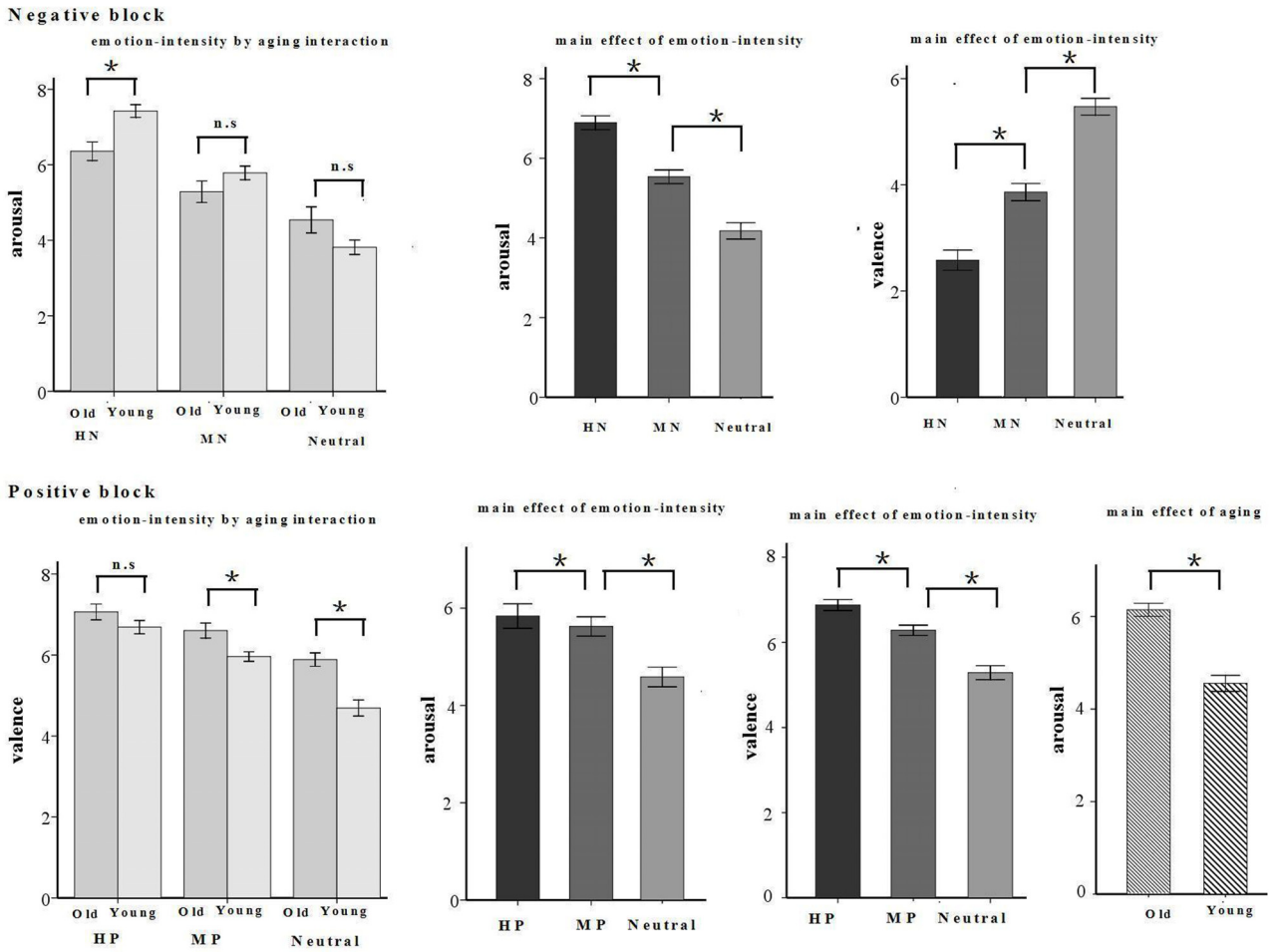

FIGURE 2 | Schematic illustration of means and SE of valence and arousal assessments given by young and old participants. *$p < 0.05$.

$[F(2,64) = 98.026, p < 0.001]$ in valence rating. HP pictures were rated more positive than were MP pictures $[F(1,32) = 67.25, p < 0.001]$ which, in turn, were rated pleasant compared with the Neutral pictures $[F(1,32) = 74.407, p < 0.05]$. The breakdown of the interaction shows that old adults rated MP $[F(1,32) = 8.537, p < 0.01]$ and Neutral $[F(1,32) = 21.215, p < 0.001]$ pictures, but not HP pictures $[F(1,32) = 2.153, p = 0.152]$, as more positive than young adults. Also, there were significant main effects of emotion intensity $[F(2,64) = 56.159, p < 0.001]$ and aging $[F(1,32) = 26.689, p < 0.001]$ in arousal rating. HP pictures were rated more arousing relative to MP pictures $[F(1,32) = 6.107, p < 0.05]$ which, again, were rated more arousing than were Neutral stimuli $[F(1,32) = 67.314, p < 0.001]$. Regardless of emotion intensity, all the pictures were rated more arousing by old adults than by young adults (see **Figure 2**).

ERP Results

P1: A repeated measures ANOVA on P1 amplitudes showed significant main effects of emotion intensity in the negative block $[F(2,64) = 10.999, p < 0.001]$ and in the positive block $[F(2,64) = 8.536, p < 0.01]$. In the negative block, both HN $[F(1,32) = 9.25, p < 0.001]$ and MN $[F(1,32) = 11.36, p < 0.001]$ stimuli elicited larger amplitudes than Neutral stimuli, while the amplitudes were similar during HN and MN conditions $[F(1,32) = 0.362, p > 0.50]$, irrespective of age groups. In the positive block, HP stimuli elicited larger amplitudes than MP $[F(1,32) = 17.137, p < 0.001]$ and Neutral stimuli $[F(1,32) = 4.976, p < 0.05]$, while the amplitudes were similar during MP and Neutral conditions $[F(1,32) = 2.652, p = 0.113]$, regardless of age groups (see **Figure 3**). Main effects of aging were not observed in the negative $[F(1,32) = 0.001, p = 0.992]$ and positive $[F(1,32) = 0.116, p = 0.735]$ blocks. No significant interaction effects between aging and emotion intensity were observed in the negative $[F(2,64) = 0.104, p = 0.895]$ and positive $[F(2,64) = 0.186, p = 0.819]$ blocks.

LPP(400–1000 ms): A repeated measure ANOVA of the LPP amplitudes was conducted with the following factors: aging, emotion intensity, frontality, and laterality in the negative block. We observed significant main effects of frontality $[F(2,64) = 48.513, p < 0.01]$ and emotion intensity $[F(2,64) = 3.983, p < 0.05]$, and a significant three-way interaction amongst frontality, emotion intensity, and aging

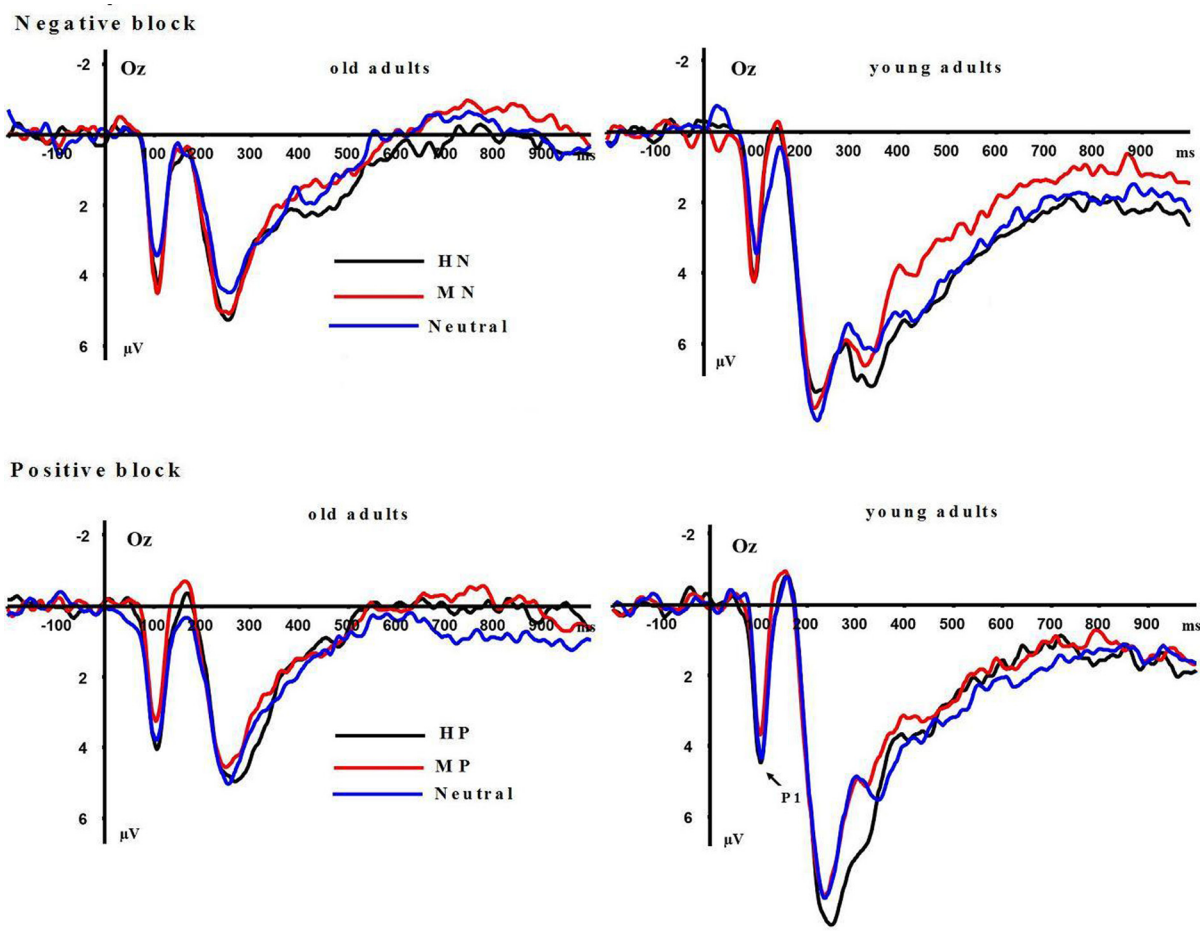

FIGURE 3 | Averaged event-related potentials (ERPs) at Oz site for highly emotional, mildly emotional, and neutral picture sets in young and old adults during positive and negative blocks.

[$F(4,128) = 6.269$, $p < 0.01$]. The breakdown of the three-way interaction showed that the interaction effect between emotion intensity and aging is significant at parietal sites [$F(2,64) = 12.11$, $p < 0.01$], but not at prefrontal sites [$F(2,64) = 0.948$, $p > 0.30$] and central sites [$F(2,64) = 0.892$, $p > 0.40$]. The analysis of interaction effect between emotion intensity and aging at parietal sites showed a significant main effect of emotion intensity in young adults [$F(2,32) = 16.042$, $p < 0.001$]. HN stimuli elicited larger amplitudes than MN stimuli [$F(1,16) = 9.374$, $p < 0.01$] which, in turn, elicited larger amplitudes than Neutral stimuli [$F(1,16) = 9.617$, $p < 0.01$]. In contrast to young adults, old adults showed no significant amplitude differences across the three conditions [$F(2,32) = 1.295$, $p > 0.20$]. Consistent with our prediction, these results suggest that the impact of aging on the brain processing of negative stimuli, as reflected in LPP, occurs at parietal scalp sites (see **Figures 4** and **5**)

Moreover, the same ANOVA model was used to test the scalp distribution of the aging by emotion intensity interaction in the positive block. We observed significant main effects of frontality [$F(2,64) = 41.808$, $p < 0.01$] and emotion intensity [$F(2,64) = 5.014$, $p < 0.05$], and a significant three-way interaction amongst frontality, emotion intensity and aging [$F(4,128) = 3.315$, $p < 0.05$]. The breakdown of the three-way interaction showed a significant interaction effect between emotion intensity and aging at prefrontal sites [$F(2,64) = 3.743$, $p < 0.05$], instead of central sites [$F(2,64) = 0.184$, $p > 0.70$] and parietal sites [$F(2,64) = 0.734$, $p > 0.40$]. The analysis of interaction effect between emotion intensity and aging at prefrontal sites showed a significant main effect of emotion intensity in old adults [$F(2,32) = 8.278$, $p < 0.05$], and HP stimuli elicited larger amplitudes than MP stimuli [$F(1,16) = 5.294$, $p < 0.05$] which, in turn, elicited larger amplitudes than Neutral stimuli [$F(1,16) = 5.736$, $p < 0.01$]. In contrast with old adults, young adults showed no significant amplitude differences across three conditions [$F(2,32) = 1.145$, $p > 0.2$]. Consistent with our prediction, these results suggest that the impact of aging on the brain processing of positive stimuli, as reflected in LPP, occurs at prefrontal sites (see **Figures 5** and **6**).

In order to explore the timing features of the above aging-related emotional intensity effects for positive stimuli in LPP amplitudes, we conducted further ANOVA of LPP

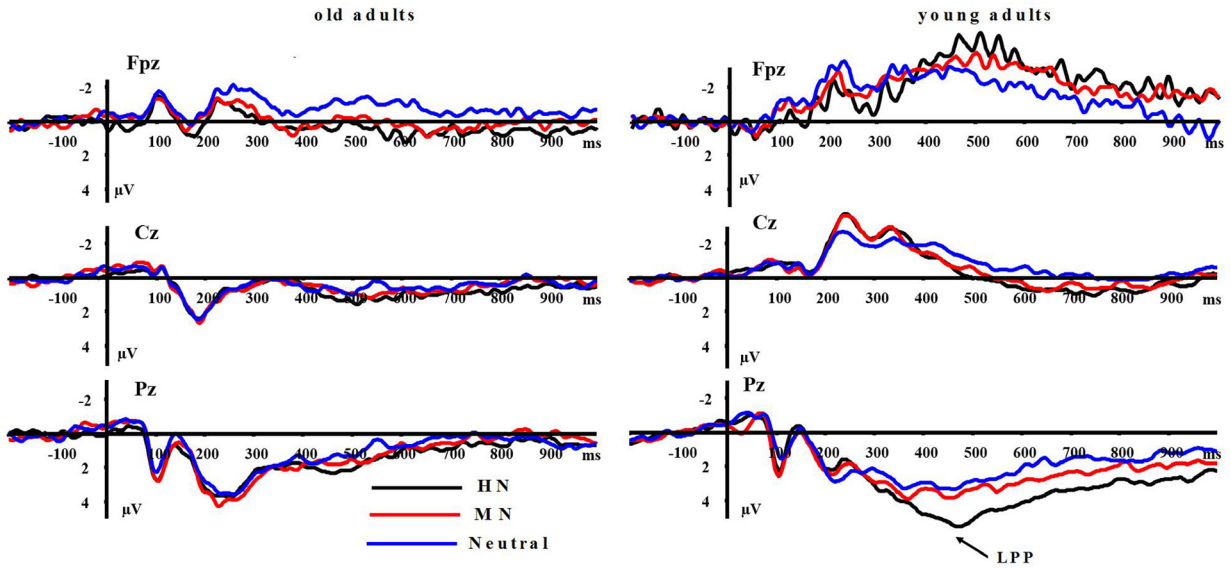

FIGURE 4 | Averaged ERPs at FPz, Cz, and Pz sites for highly positive (HP), mildly positive (MP), and neutral stimuli in young and old adults.

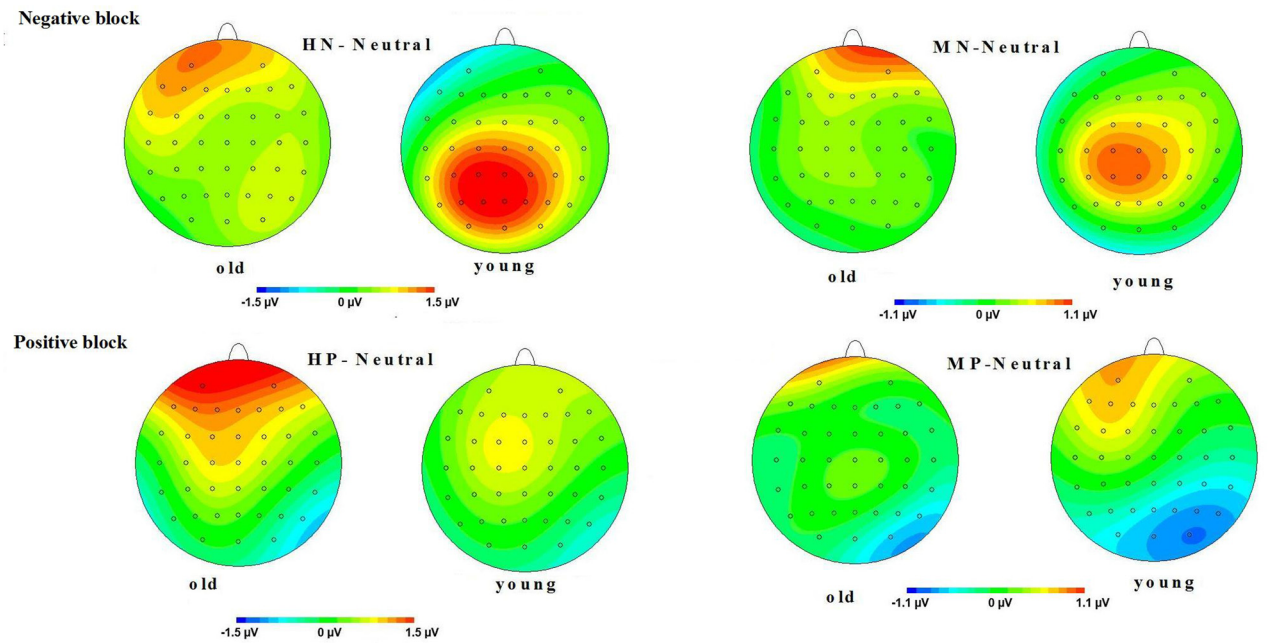

FIGURE 5 | (Top) Topographical maps of the mean amplitudes difference (across 500–800 ms) between highly negative (HN) and neutral stimuli, and between mildly (MN) and neutral stimuli in old and young adults. **(Bottom)** Topographical maps of the mean amplitudes difference (across 500–800 ms) between HP and neutral stimuli, and between MP and neutral stimuli in old and young adults.

amplitudes at prefrontal region with the following factors: aging (two levels), emotion intensity (three levels) and timing (three levels: 400–600 ms, 600–800 ms, 800–1000 ms). The results showed no significant three-way interaction effect amongst aging, timing and emotion intensity [$F(4,128) = 2.544$, $p > 0.05$] in the positive block. In the positive block, the aging by emotion intensity interaction was similarly significant in 400–600 ms [$F(2,64) = 4.388$, $p < 0.05$], 600–800 ms [$F(2,64) = 3.408$, $p < 0.05$] and 800–1000 ms [$F(2,64) = 4.619$, $p < 0.05$].

Also, the same analysis was used for LPP amplitudes in the negative block. The results showed no significant three-way interaction amongst aging, timing and emotion intensity [$F(4,128) = 1.121$, $p > 0.3$]. Similarly, the two-way interaction

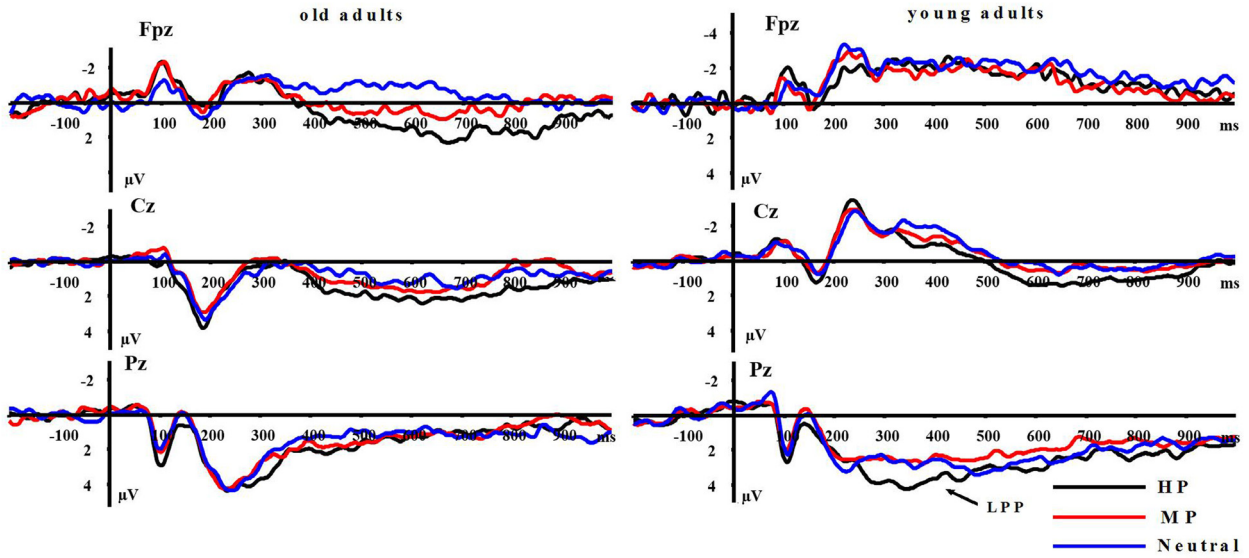

FIGURE 6 | Averaged ERPs at FPz, Cz, and Pz sites for HP, MP, and neutral stimuli in young and old adults.

between aging and emotion intensity was similarly significant in 400–600 ms [$F(2,64) = 3.966$, $p < 0.05$], 600–800 ms [$F(2,64) = 4.384$, $p < 0.05$] and 800–1000 ms [$F(2,64) = 3.811$, $p < 0.05$].

These results suggest that the aging-related emotional effects in LPP amplitudes exist reliably, unaffected by the time windows of LPP quantification.

Is the Aging-Related Emotion Effect Specific to Late Processing Stage?

The above results implied that the impact of aging on brain responding to positive and negative stimuli of varying emotional intensities was significant in LPP but not in P1 stage. In order to test the reliability of this timing effect, we conducted an ANOVA with timing (two levels: P1 and LPP), aging (two levels: young and old) and emotion intensity (three levels: high, mild, and neutral) as factors, in the negative block and in the positive block, respectively. The results showed a significant three-way interaction amongst timing, aging and emotion intensity in the positive [$F(2,64) = 3.681$, $p < 0.05$] block with the aging by emotion intensity interaction significant at LPP but not in P1 amplitudes. Similarly, there was a significant three-way interaction involving timing, aging and emotion intensity in the negative block [$F(2,64) = 3.785$, $p < 0.05$], with the aging by emotion intensity interaction significant in LPP but not in P1 amplitudes. These results confirmed that the impact of aging on brain processing of negative and positive stimuli was specific to late rather than early processing stage.

Perceived Frequency Report

Firstly, all subjects ($n = 34$) reported the perception of negative pictures in the negative block and positive pictures in the positive block, respectively.

In the negative block, the perceived frequency of negative pictures was higher in young (72.9%) relative to old adults [42.9%; $F(1,32) = 6.571$, $p < 0.05$, see **Figure 7**]. This suggests that negative stimuli influenced young adults to a greater extent compared to old adults. We included all the participants and conducted a correlation analysis between the perceived frequency and the composite emotion effect at P1 and LPP components. The composite emotion effect was defined as the average of the emotion effect for HN and MN stimuli, which was calculated as the amplitude differences between negative and neutral conditions collapsed across the corresponding electrode sites (three occipital sites for P1, and three parietal sites for LPP). The result showed a significant positive correlation between the composite emotion effect in LPP amplitudes and the perceived frequency of negative pictures ($r = 0.368$, $p < 0.05$, see **Figure 8**), whereas the correlation between the perceived frequency and the composite emotion effect in P1 amplitudes was not significant ($r = 0.115$, $p = 0.517$). This suggests that the LPP amplitude may be a unique reflection of the subjective emotion effect in the current study. Therefore, ERP data and the behavioral data both displayed decreased negative emotional effect in old adults than in young adults.

In the positive block, the perceived frequency of positive pictures was higher in old adults (70%) compared to young adults [57.1%; $F(1,32) = 67.161$, $p < 0.01$; see **Figure 7**]. This suggests that old adults may have experienced more pleasant feelings for positive pictures than young adults. In addition, we conducted a correlation analysis between the perceived frequency and the composite emotion effect in LPP amplitudes. The composite emotion effect was defined as the average of the emotion effect for HP and MP stimuli, which was calculated as the amplitude differences between positive and neutral conditions collapsed across the corresponding electrode sites (three occipital sites for P1, and three prefrontal sites for

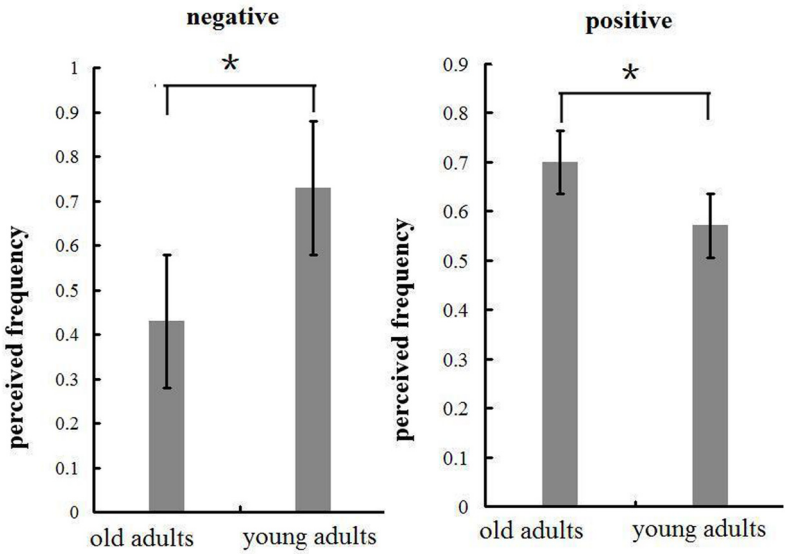

FIGURE 7 | Means and SE of perceived frequency of the emotional pictures in negative and positive blocks. $^{*}p < 0.05$.

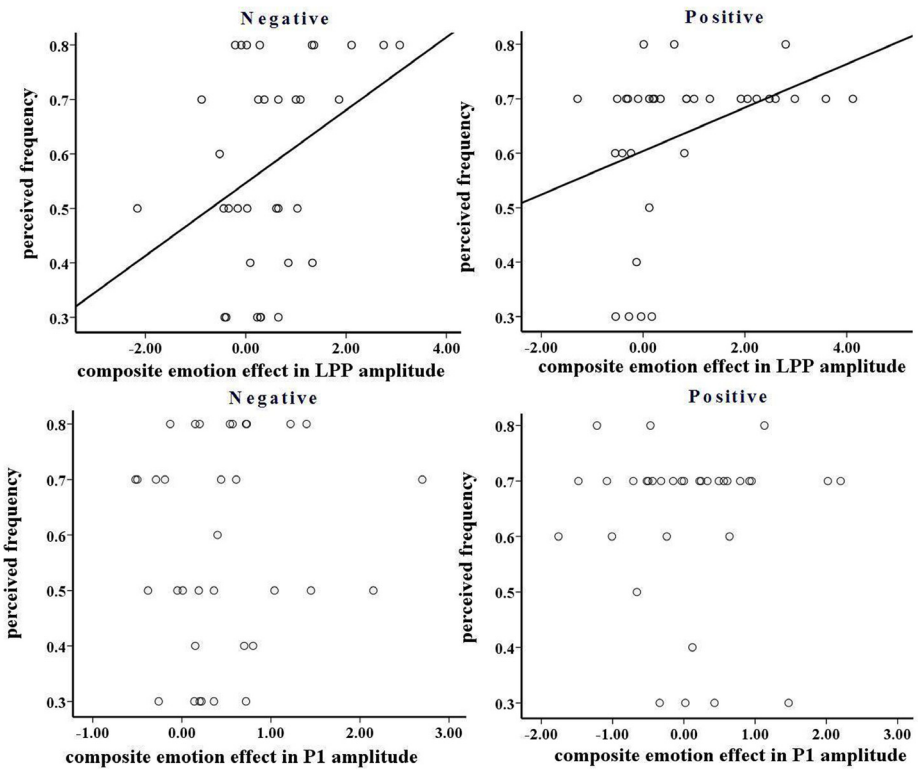

FIGURE 8 | (Top) The correlation between composite emotion effect in late positive potentials (LPP) amplitude and perceived frequency in negative and positive blocks. **(Bottom)** The correlation between composite emotion effect in P1 amplitude and perceived frequency in negative and positive blocks.

LPP). The analysis showed a significantly positive correlation between the composite emotion effect in LPP amplitudes and the perceived frequency data ($r = 0.371$, $p < 0.05$, see **Figure 8**), whereas the correlation between the emotion effect in P1 amplitudes and the perceived frequency was statistically non-significant ($r = -0.038$, $p = 0.832$), suggesting that the LPP amplitude is probably a unique reflection of the subjective emotional effect for positive stimuli. Therefore, both ERP data

and the behavioral data displayed increased positive effect in old adults than in young adults.

Discussion

P1 component is an early component peaking about 100 ms post stimulus, and it has been accepted to reflect exogenous and automatic sensory processing (Scott et al., 2009; Dan and Raz, 2012). P1 amplitudes are thought to be sensitive to attention allocation (Luck et al., 1994; Smith et al., 2003; Brown et al., 2010), and be heightened for emotional stimuli compared to neutral stimuli (Scott et al., 2009; Dan and Raz, 2012). We observed a significant emotion intensity effect but not significant emotion intensity by aging interaction for P1 amplitudes, in both positive and negative blocks. Both young and old adults showed larger amplitudes for HN and MN stimuli relative to neutral stimuli. This suggests that negative stimuli elicited an enhanced allocation of early sensory attention in both samples, and this early visual encoding of negative stimuli was similar for both groups. This result is in line with a couple of studies reporting no aging effect in early encoding of threatening information (Hahn et al., 2006; Mather and Knight, 2006), and is supported by the evidences that the aging-related positive effect results from the controlled instead of the automatic processing stage (Mather and Knight, 2006; Leclerc and Kensinger, 2008b). On the other hand, HP stimuli elicited larger P1 amplitudes compared to Neutral stimuli in both samples, and there was also no significant emotion intensity × aging interaction in P1 amplitudes for the positive block. This suggests that HP stimuli elicited enhanced early visual attention than neutral stimuli, consistent with prior findings (Holmes et al., 2009; Yuan et al., 2014a) and this enhancement was similar for young and old adults. This finding is consistent with prior behavioral studies suggesting that old adults, like young adults, showed a rapid detection of arousing information, irrespective of valence (Hahn et al., 2006; Mather and Knight, 2006; Leclerc and Kensinger, 2008b).

It is worth noting that, previous studies showed an impact of visual acuity on the processing of emotional stimuli (Butler et al., 2009). Although all the subjects reported no visual problems and found no difficulty reading textual instructions on the monitor at a distance of 2.5 m, it is still a question whether visual acuity in old adults is different from that in young adults, and whether visual acuity is an alternative interpretation of our results, as we had no quantitative measurement of visual acuity across groups. However, if visual acuity in old adults differs from that in young adults, we should have observed a significant aging effect in P1 amplitude, which has been established to reflect early visual processing of stimuli (Scott et al., 2009; Dan and Raz, 2012). However, the present study observed neither main effect of aging, nor aging by emotion intensity interaction, suggesting that the visual acuity was most likely not significantly different across old and young adults.

Distinct from P1 analysis, the analysis of LPP amplitudes showed a significant block, emotion intensity, and aging interaction. LPP amplitudes increased with negative intensity in young adults, but not in old adults. LPP activity is considered to reflect consciously controlled processing of stimulus meanings (Wood and Kisley, 2006; Kisley et al., 2007). The LPP amplitudes have been shown to increase with the allocation of voluntary attention to emotional stimuli (Hajcak and Dennis, 2009; Langeslag and Van Strien, 2010). This association is confirmed by our findings of a significant correlation between the emotion effect in LPP amplitudes and the perceived frequency of negative pictures. Young adults displayed prominent emotion effects for HN stimuli and, of a smaller size, for MN stimuli, while old adults showed no emotion effect for these stimuli. Though this result is supported by our behavioral findings that young adults reported more perception of negative stimuli than old adults, this result appears inconsistent with previous studies that old adults exhibited larger LPP amplitudes for negative compared to neutral stimuli in emotional assessment tasks (Wood and Kisley, 2006; Kisley et al., 2007). It is worth noting that the current study used a non-emotional distracting task, which might have facilitated old adults disengaging attention from negative stimuli, thus leading to reduced brain reactions to these stimuli (Isaacowitz et al., 2006a,b; Mauss et al., 2007). This hypothesis needs to be directly explored in future studies by testing the impact of aging on the attentional disengagement from negative stimuli.

However, the above findings are consistent with the following abundant evidences. It has been reported that old adults are better than young adults in sustaining positive emotions and terminating negative emotions (Carstensen et al., 2000). For example, Carstensen et al. (2000) observed that old adults had greater ability of differentiating between distinct categories of emotions than did young adults, which was thought to be linked with less neuroticism and better emotion control. This is consistent with later studies suggesting that aging is associated with habitual attention shifting from negative to positive cues (Carstensen and Mikels, 2005; Isaacowitz et al., 2006a). One explanation for these phenomena is that in their age advancement process old adults might have learned more about dealing with negative events, consequently they could spend less time on negative events when compared with young adults (Scheibe and Carstensen, 2010).

On the other hand, this study observed increasing LPP amplitudes with the pleasant intensity of positive stimuli in old adults, where young adults showed no significant emotional effects for HP and MP stimuli. This aging-related difference was observed in prefrontal but not central and parietal regions. Leclerc and Kensinger (2008a) observed greater neural activations of old adults, but not young adults, for positive compared to negative pictures in ventromedial prefrontal cortex during the analysis of picture meanings. Consistent with this finding, Ritchey et al. (2011) observed enhanced ventrolateral and medial prefrontal cortex activity in response to positive versus negative stimuli in old adults, during elaborative processing of picture meanings. Also, recent studies have shown that the function of Anterior Cingulated Cortex (ACC) is well-maintained in old adults (Fjell et al., 2009), and the engagement of rostral ACC in voluntary attention for happy faces is correlated with the old adults' emotional stability (Brassen et al., 2011). These evidences suggest that prefrontal cortical regions play a critical role in old adults' enhanced cognitive processing of

pleasant stimulus meanings. As stated above, LPP represents elaborative, cognitive processing of stimulus meanings with voluntary attention to emotional stimuli (Kisley et al., 2007; Hajcak and Dennis, 2009; Langeslag and Van Strien, 2010). This probably explains why old adults exhibited enhanced LPP amplitudes for positive relative to neutral stimuli in prefrontal but not other scalp regions. In addition, the old adults' enhanced LPP amplitude for positive stimuli probably reflects increased positive emotion induction, as evidenced by the higher frequency report of positive stimuli in old versus young adults, and by the positive correlation between LPP and the perceived frequency of positive pictures. Also, this argument is supported by the positive correlation between LPP amplitudes and emotion experience in many prior studies (Hajcak and Nieuwenhuis, 2006; Flaisch et al., 2008; MacNamara et al., 2011; Yuan et al., 2014a). These behavioral and electrophysiological data consistently suggest that the old adults may have experienced more positive emotions than young adults, though the two samples viewed the same pictures.

The current study used a distracting task which required subjects to count the number of pictures, irrespective of emotionality. This means that emotional processing was unlikely to have happened with full involvement of cognitive resources; but evidently, it may have occurred in the service of conscious perception and controlled processing resources. Under such a task setting, the current study observed aging by emotion interactions in LPP but not in P1 amplitudes. These results suggest that, observing an aging-related positivity effect may not request full cognitive resources, but instead just requires the involvement of conscious awareness. This view is in line with many studies reporting that old adults show an attentional preference for positive stimuli and attention disengagement from negative stimuli, once the emotional nature of the stimulus has been discerned (Isaacowitz et al., 2006b; Allard and Isaacowitz, 2008; Leclerc and Kensinger, 2008b; Allard et al., 2010).

The aging-related differences in LPP amplitudes for emotional stimuli may be explained by SST (Carstensen, 1992; Carstensen et al., 2000). This theory posits that young adults perceive their time remaining in life to be expansive and are motivated to acquire knowledge, whereas old adults perceive their time left in life as limited thus prioritize present-oriented emotional meanings. This motivational shift leads old adults to focus more on positive aspect of life. However, it has yet to be determined whether changes in time perspective do, as proposed by SST, serve as a mechanism mediating the enhanced attention of old adults to positive information. This issue needs to be explored in future studies by testing the mediation of time perspective in the association between aging and the LPP responding to emotional stimuli.

Conclusion

By using ERP technique and a block-design covert emotional task, the present study investigated neural mechanisms underlying the aging-related enhancement of positive affects. Although the same number of emotional pictures was presented for young and old adults in each block, old adults reported more perception of positive stimuli and less perception of negative stimuli than young adults. ERP results showed larger LPP amplitudes for HN and MN stimuli compared to neutral stimuli in young adults, but not in old adults. By contrast, old adults displayed significant emotion effects for HP and MP stimuli in LPP amplitudes, both of which were absent in young adults. These results were supported by the post-experiment stimulus assessment, which showed more positive ratings of Neutral and MP stimuli, and reduced arousal ratings of HN stimuli in old compared to young adults. These behavioral and electrophysiological data consistently suggest that aging is linked with enhanced attention bias for positive stimuli and reduced susceptibility to negative stimuli, which might contribute to the enhanced positive affects and LS (see the Supplementary Material) in old relative to young adults.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2015.00143

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Identification Numbers of CAPS Pictures Presented in this Study

HN:142,146,147,148,149,150,152,173,179,193,196,205,218,222,232,240,243,246,248,254,255,256,268,269,276,280,281,282,283,284,443,458,471,484,502,511,522,528,532,533,536,539,540,541,542,555,559,569,571,572,573,577,580,583,590,597.

MN:153,155,157,161,166,169,171,184,186,195,197,198,200,204,213,223,227,228,241,242,247,259,260,263,274,363,456,462,466,480,507,512,519,520,524,526,531,546,549,550,552,563,567,581,588,591,592,595,599,607,609,612,613,615,621,625.

Neutral(negative):295,297,298,304,307,311,312,313,315,316,319,320,322,324,329,347,367,372,386,387,389,393,396,398,403,407,411,419,422,425,426,436,455,465,490,649,658,673,674,682,705,706,709,723,725,726,733,735,742,744,745,747,768,808,826,834.

MP:1,2,21,460,848,5,34,38,41,50,58,60,61,63,71,87,111,119,123,137,291,294,299,300,339,357,377,438,446,454,501,635,643,645,757,764,765,766,787,788,789,802,810,850,8,19,24,32,33,47,54,68,82,309,680,689.

HP:28,4,7,10,11,12,13,14,15,16,18,20,43,52,53,57,88,94,98,99,101,102,109,118,121,129,463,478,486,488,491,663,675,691,701,718,749,750,752,756,762,775,776,780,781,791,44,45,461,487,640,641,642,800,813,822.

Neutral(positive):235,258,292,293,295,298,302,305,833,310,311,318,320,327,329,336,355,381,382,386,387,403,406,410,424,436,451,464,479,503,665,747,767,768,778,831,849,851,459,469,504,510,514,829,517,523,534,603,601,719,732,763,746,785,842,839.

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REVIEW
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Biomarkers of postoperative delirium and cognitive dysfunction

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Elderly surgical patients frequently experience postoperative delirium (POD) and the subsequent development of postoperative cognitive dysfunction (POCD). Clinical features include deterioration in cognition, disturbance in attention and reduced awareness of the environment and result in higher morbidity, mortality and greater utilization of social financial assistance. The aging Western societies can expect an increase in the incidence of POD and POCD. The underlying pathophysiological mechanisms have been studied on the molecular level albeit with unsatisfying small research efforts given their societal burden. Here, we review the known physiological and immunological changes and genetic risk factors, identify candidates for further studies and integrate the information into a draft network for exploration on a systems level. The pathogenesis of these postoperative cognitive impairments is multifactorial; application of integrated systems biology has the potential to reconstruct the underlying network of molecular mechanisms and help in the identification of prognostic and diagnostic biomarkers.

Keywords: postoperative delirium, postoperative cognitive dysfunction, biomarker, systems biology, POD, POCD

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Introduction

More than 40% of surgical procedures in the US are performed on patients aged 65 and over Control Prevention Centers for Disease (2010). Elderly patients frequently experience postoperative cognitive impairment, characterized by progressive cognitive and sensory decline. An acute phase of cognitive impairment is postoperative delirium (POD; according to DSM-5: 293.0 "Delirium Due to Another Medical Condition"; Rudolph et al., 2008a). Deliria are further classified by duration and level of activity such as hyperactive, hypoactive or mixed. Patients with POD frequently develop a chronic phase of cognitive impairment, i.e., postoperative cognitive dysfunction (POCD; according to DSM-5: 294.10/11 "Major Neurocognitive Disorder Due to Another Medical Condition Without/With Behavioral Disturbance" or 331.83 "Mild Neurocognitive Disorder Due to Another Medical Condition"; Rudolph et al., 2008a). POCD is developed in 32% of patients with short delirium duration (1–2 days) and in 55% of patients with longer delirium (Rudolph et al., 2008a). The incidence of POD/POCD varies depending on the study and type of surgery; as illustrated on **Figure 1**, POD incidence ranges from 13.2% to 41.7% and POCD incidence ranges from 8.9% to 46.1%. The prevalence of POD and POCD is associated with higher mortality, increased incidence of postoperative complications, longer duration of hospital stay, greater utilization of social financial assistance and earlier retirement (Greene et al., 2009; Robinson et al., 2009; Steinmetz et al., 2009; Ansaloni et al., 2010; Liu et al., 2013). Patients older than 65 are predisposed to POD and POCD if they have hypoalbuminemia,

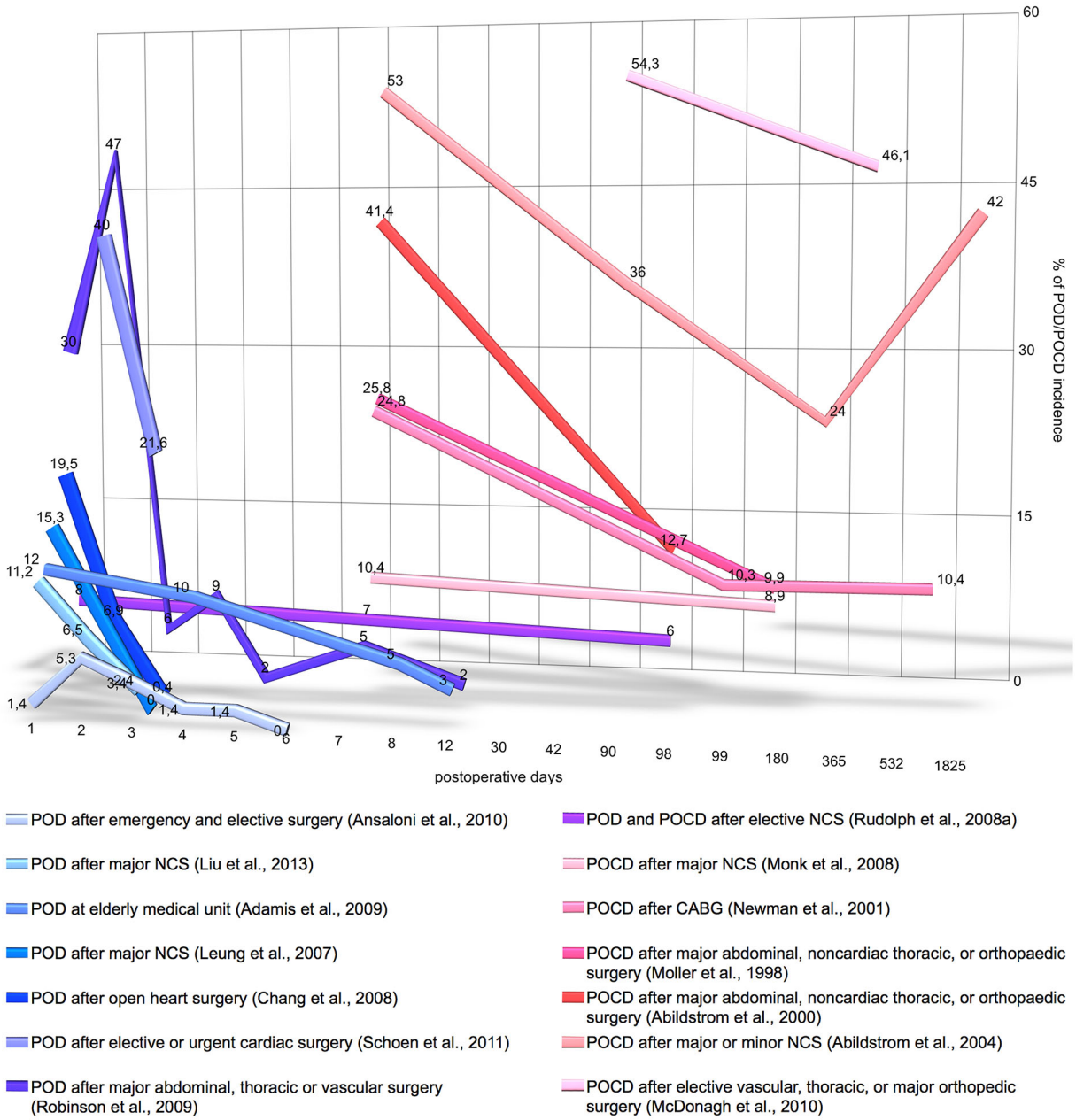

FIGURE 1 | Incidence and time-course of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) incidence. *Y*-axis denotes the percentage on POD/POCD incidence registered by the different studies. *X*-axis denotes the number postoperative days on logarithmic scale. The graph does not include the data of POD/POCD incidence, if it was measured only once postoperatively, if measurement time was not precisely stated or the study includes less than 140 patients. CABG, coronary artery bypass grafting; NCS, noncardiac surgery.

abnormal preoperative serum sodium, potassium, glucose or blood sugar levels as well as psychopathological symptoms, alcohol abuse or co-morbidities (Moller et al., 1998; Abildstrom et al., 2000; Newman et al., 2001; Chang et al., 2008; Monk et al., 2008; Deiner and Silverstein, 2009; Ansaloni et al., 2010; Kazmierski et al., 2014b). The cognitive status of elderly patients including depression, dementia or cognitive impairment is a significant risk factor for development of POD (Elie et al., 1998; Leung et al., 2005; Minden et al., 2005; Inouye, 2006; McAvay et al., 2007; Greene et al., 2009; Kosar et al., 2014). For instance, dementia is a significant risk factor that increases delirium occurrence risk by fivefold (Elie et al., 1998); *vice versa*, delirium itself may lead to dementia and long-term cognitive deterioration (Jackson et al., 2004).

Postoperative delirium is defined in DSM-5 by several criteria including clouding of consciousness with reduced

awareness of environment and difficulty in sustaining and/or shifting attention. In addition, POD is characterized by changes in cognition that affect memory, language and orientation in time/space (American Psychiatric Association, 2013). The impairment of memory, perceptual-motor abilities, language and attention are transit characteristics between POD and POCD. Memory impairment significantly affects cognitive decline and leads to impaired social and professional functioning in POCD patients. Memory deterioration lasting more than 1 month signifies the entry into the chronic phase of the cognitive impairment (American Psychiatric Association, 2013). POCD following delirium might increase the rate of cognitive deterioration in Alzheimer's disease (Gross et al., 2012). Specific characteristics of POCD include decline in speed of processing the information and disturbance in executive functioning but the patient typically remains oriented to person, time and space (Tsai et al., 2010). The decline in POCD is mostly recognized by comparison to the patient's pre-operative capabilities (Deiner and Silverstein, 2009). Delirium is usually measured by standardized clinical tests such as the Confusion Assessment Method (Inouye et al., 1990).

To improve diagnosis and treatment of POD/POCD, research aimed to identify prognostic and diagnostic biological markers. Biomarkers can determine severity and phase of the cognitive impairment, stratify patients who are likely to respond to specific treatment and monitor the efficiency of the treatment. Genetic markers (Papadopoulou et al., 2006), RNA (Sørensen and Ørntoft, 2010) and microRNA (Scherzer et al., 2007) levels, proteins (Wang et al., 2005), and post-translational changes such as glycosylation (Norton et al., 2008; Drake et al., 2010) and phosphorylation (Deguchi et al., 2002), have been demonstrated as prognostic biomarkers in a variety of diseases including disorders of the central nervous system (CNS) and these biochemical entities should be considered as possible markers for POD and POCD.

The most prominent hypothesis for the molecular mechanisms of POD and POCD is a central cholinergic deficiency caused by deregulation of cholinergic anti-inflammatory pathways leading to increased inflammation (Inouye, 2006). Despite detection of decreased acetylcholine levels, several studies reported contradictory findings regarding levels of serum anticholinergic activity (SAA; see Section Biological Markers of Postoperative Delirium). Another suggestion is that delirium is caused by a combination of dopamine excess and acetylcholine deficiency (Trzepacz, 2000). Low tryptophan levels can be associated with delirium via decreased synthesis of brain serotonin or alteration of melatonin production, which has been challenged (see Section Biological Markers of Postoperative Delirium). The association between POD/POCD and pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1beta, interleukin-6 and interleukin-8, neuronal injury marker and C-reactive protein was shown by several studies and questioned by others (see Sections Biological Markers of Postoperative Delirium and Common Biomarkers of Postoperative Delirium and Cognitive Dysfunction for Details). Some POD/POCD patients have elevation in serum cortisol levels that may be explained by genetic variation of the glucocorticoid receptor gene (Perroud et al., 2011). The isoforms of apolipoprotein E can provoke cholinergic deficiency and acetylcholinesterase unblocking (Soininen et al., 1995), although some results are contradicting. The amyloid beta peptide associated with Alzheimer's disease was also observed in the serum of POCD patients. These and other findings are discussed in details in Sections Biological Markers of Postoperative Delirium, Common Biomarkers of Postoperative Delirium and Cognitive Dysfunction and Biological Markers of Postoperative Cognitive Dysfunction.

Here we review the known genetic risk factors and physiological and immunological changes that have been associated with POD and POCD. Deiner and Silverstein reviewed the postoperative delirium and cognitive dysfunction in 2009. More recent reviews discussed biomarkers and genetic variance for delirium alone (Khan et al., 2011; Stoicea et al., 2014). This article comprises a literature review on both POD and POCD biomarkers with a focus on recent findings. The current knowledge about the contributing biomarkers to postoperative delirium and cognitive dysfunction is summarized in **Figure 2.** POD and POCD have a wide range of contributing mechanisms and some biomarkers are overlapping. A more detailed description of the known and potentially novel biomarkers is provided below.

Biological Markers of Postoperative Delirium

The leading hypothesis suggests that delirium can be caused by a central cholinergic deficiency (Inouye, 2006) and is based on treatment with drugs which impair cholinergic function (Tune et al., 1981). The impact on muscarinic anticholinergic burden can be measured by SAA (Plaschke et al., 2007b). Increase of SAA levels is correlated with greater number of delirium symptoms, whereas SAA decrease is correlated with delirium resolution (Mach et al., 1995; Flacker et al., 1998; Mussi et al., 1999). Several studies questioned the association between SAA and delirium, considering that a temporal profile of SAA can be influenced by pre-existing cognitive impairment, infection or illness (Flacker and Lipsitz, 1999; Plaschke et al., 2007a; van Munster et al., 2012). The impact of drugs on the cholinergic system was addressed in detail by Fox et al. (2014) and Praticò et al. (2005).

Acetylcholine plays an important role in memory, associative learning and selective attention (Hasselmo, 1995; Everitt and Robbins, 1997). Impairment of its receptors, such as nicotinic and muscarinic acetylcholine receptors, might lead to cholinergic deficiency and delirium development (Hshieh et al., 2008). Postsynaptic M1 muscarinic receptors are predominantly expressed in hippocampus, cerebral cortex and striatum (Hersch et al., 1994; Levey, 1996) and play a role in cognitive functioning, memory and learning (Anagnostaras et al., 2003; Volpicelli and Levey, 2004; Fisher, 2008). Inhibition of the M1 muscarinic receptor was hypothesized to cause POD and POCD (Praticò et al., 2005). Inhibition of postsynaptic nicotinic receptors by

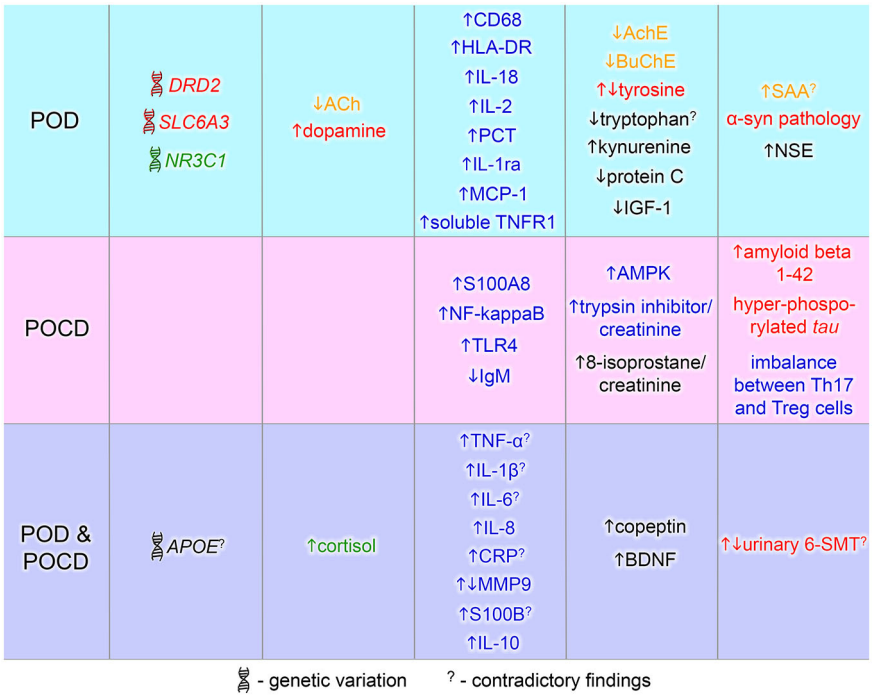

FIGURE 2 | Biomarkers of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). Biomarkers identified in POD or POCD patients are in blue and pink area respectively. The common POD/POCD biomarkers are presented in the violet area. Font color denotes a marker type: red—dopamine-related marker, green—glucocorticoid-related marker, yellow—cholinergic marker, blue—inflammation-related marker, black—others. 6-SMT, 6-sulfatoxymelatonin; ACh, acetylcholine; AchE, acetylcholinesterase; AMPK, 5′ adenosine monophosphate-activated protein kinase; *APOE*, apolipoprotein E; BDNF, brain-derived neurotrophic factor; BuChE, butyrylcholinesterase; CD68, cluster of differentiation 68; CRP, C-reactive protein; *DRD2*, dopamine receptor D2; HLA-DR, human leukocyte antigen-DR; IGF-1, insulin growth factor-1; IgM, immunoglobulin M; IL, interleukin; MCP-1, monocyte chemotactic protein 1; MMP9, matrix metalloproteinase-9; NF-kappaB, nuclear factor kappa B; *NR3C1*, nuclear receptor family 3, group C, member 1; NSE, neuron specific enolase; PCT, procalcitonin; S100A8, S100 calcium binding protein A8 (myeloid-related protein-8, calgranulin A); S100B, S100 calcium binding protein B; SAA, serum anticholinergic activity; *SLC6A3*, solute carrier family 6, member 3; Th17, T helper 17 cells; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor-1; Treg, regulatory T cells; α-syn, alpha-synuclein.

isoflurane and nitrous oxide results in learning and memory impairment after surgery (Culley et al., 2003; Kong et al., 2015). Vice versa, agonists of the nicotinic receptors can improve cognitive function (Wagner et al., 2013): activation of the nicotinic acetylcholine receptor alpha 7 prevents the cognitive decline after surgery by inhibition of NF-kappaB (nuclear factor kappa B) activation and suppression of macrophage migration into the hippocampus (Terrando et al., 2011). This phenomenon shows the bidirectional communication between the nervous and the immune system (Ader et al., 1995). Therefore, acetylcholine and its receptors are likely contributors to the onset of POD and POCD.

The cholinergic anti-inflammatory pathway, mediated by acetylcholine, is associated with neurocognitive decline (Ramlawi et al., 2006). It suppresses NF-kappaB activation and inhibits the release of inflammatory cytokines (e.g., tumor necrosis factor, interleukin (IL)-1β, IL-6, and IL-18) but not IL-10, an anti-inflammatory cytokine (Borovikova et al., 2000; van Gool et al., 2010). Septic and aseptic inflammation can trigger acute cognitive deficits in patients with cholinergic system depletion (Field et al., 2012). Acetylcholinesterase and butyrylcholinesterase inactivate acetylcholine through hydrolysis, possibly enhancing inflammation. Decreased cholinesterase activity in delirious patients was correlated with elevated levels of C-reactive protein and IL-6 (Cerejeira et al., 2012). C-reactive protein (CRP) is a marker of nonspecific acute-phase response in inflammation, infection and tissue damage (Pepys and Hirschfield, 2003), correlated with cognitive decline (Tilvis et al., 2004). The association between high CRP levels and delirium was shown by several studies (Beloosesky et al., 2004; Macdonald et al., 2007; Burkhart et al., 2010; Pol et al., 2014; Ritchie et al., 2014; Zhang et al., 2014b), and questioned by others (Lemstra et al., 2008; Girard et al., 2012).

An inflammatory response to postoperative stress may contribute to delirium via disruption of the blood-brain barrier (Rudolph et al., 2008b). The increased risk is correlated with elevated monocyte chemotactic protein 1, procalcitonin, human leukocyte antigen-DR, CD68, IL-1β, IL-6, IL-8, IL-18 and anti-inflammatory IL-1 receptor antagonist (van Munster et al., 2008,

2011a; van den Boogaard et al., 2011; Cape et al., 2014). Elevated levels of the pro-inflammatory cytokines IL-2 and tumor necrosis factor-α (TNF-α) were detected in the POD patients who had undergone coronary artery bypass graft surgery (Kazmierski et al., 2014a,b). Inhibition of inflammatory IL-12/IL-23-mediated pathways may reduce Alzheimer's disease pathology and reverse cognitive deficits in aged mice (Vom Berg et al., 2012). van Munster et al. (2011b) observed high levels of IL-8 and cortisol before a delirium onset and high levels of IL-6 and S100 calcium-binding protein B (S100B) in the course of delirium but functional genetic variations in interleukin-6 gene (*IL6*), interleukin-6 receptor gene (*IL6R*) and interleukin-8 gene (*IL8*) were not associated with delirium (van Munster et al., 2011b). Likewise, the association between delirium and higher IL-1, IL-6 and TNF-α plasma levels was not confirmed (Adamis et al., 2007, 2009). The lower plasma concentrations of the coagulation marker protein C together with elevated plasma concentrations of soluble tumor necrosis factor receptor-1 were associated with increased risk for delirium (Girard et al., 2012).

S100B is an indicator of the direct neuronal injury, e.g., by cerebrovascular accidents and traumatic brain injury (Berger et al., 2005). Several studies consistently demonstrated highly elevated levels of S100B in patients with delirium (Pfister et al., 2008; van Munster et al., 2009b, 2010a,c; van den Boogaard et al., 2011). Grandi et al. (2011) found no difference in levels of S100B in delirious and control patients. The same study indicated that neuron-specific enolase and brain-derived neurotrophic factor (BDNF) could be potential biomarkers for delirium in intensive care unit patients (Grandi et al., 2011). BDNF plays role in synaptic plasticity, neuronal survival, differentiation and growth (Acheson et al., 1995; Huang and Reichardt, 2001). Similarly to BDNF, insulin growth factor-1 (IGF-1) promotes neuronal proliferation, development, survival and enhanced synaptic transmission in CNS (Frost et al., 2003; Shcheglovitov et al., 2013; Huat et al., 2014). Tumor necrosis factor-α (TNF-α) can be involved in neurodegeneration through inhibition of IGF-1 (Frost et al., 2003; Bassil et al., 2014). Low baseline levels of IGF-1 were associated with an increased risk of delirium incidence (Wilson et al., 2005; Adamis et al., 2007, 2009). Due to the neuroprotective function, low levels of IGF-1 may have a significant effect on delirium severity (Adamis et al., 2009). Understanding the complex connection between the cholinergic system and increased pro-inflammatory response as well as neurodegeneration is likely to shed light on the molecular and cellular causes of delirium.

Another popular hypothesis suggests that delirium can be caused by dopamine excess and acetylcholine deficiency relative and/or absolute to each other (Trzepacz, 2000). Cytokines can disrupt the neurotransmitter system balance, leading to reduced acetylcholine release (Willard et al., 1999) and increased dopamine and norepinephrine release (Stefano et al., 1994). Delirium, related to anticholinergic mechanisms, was successfully treated with the dopamine receptor antagonists (Alagiakrishnan and Wiens, 2004). One of such receptors is dopamine receptor D2 (DRD2); its dysfunction leads to hallucinations, impairment of motor and frontal lobe functions (Volkow et al., 1998; Makoff et al., 2000). The gene encoding for D_2 subtype of dopamine receptor (*DRD2*) was associated with schizophrenia and movement disorders (Kukreti et al., 2006; Koning et al., 2012). Seven single nucleotide polymorphisms (SNPs) in the *SLC6A3* (solute carrier family 6, member 3) gene and three genetic polymorphisms in the *DRD2* gene are associated with delirium (van Munster et al., 2010d). The *SLC6A3* gene is coding for the dopamine transporter, hence variation of this gene can lead to a lower concentration of cerebral basal dopamine, diminishing the risk of delirium (van Munster et al., 2010b). One of the detected genetic polymorphisms in *SLC6A3* was associated with pediatric bipolar disorder (Mick et al., 2008); although no connection was found between bipolar disorder in adults and postoperative delirium.

Apolipoprotein E (ApoE) regulates the cholesterol metabolism, participates in repairing and maintaining of neuronal membranes and myelin during development and after injury (Ignatius et al., 1986). It is responsible for cholinergic neuron destruction by increased synthesis and defective clearance of amyloid beta (Kowall et al., 1991). Different isoforms of *APOE* gene can provoke cholinergic deficiency and acetylcholinesterase unblocking (Soininen et al., 1995). The carriers of *APOE* ε4 allele have greater risk of delirium development (Adamis et al., 2007; Leung et al., 2007; van Munster et al., 2009a) and are more predisposed to cellular damage within the brain (Olivecrona and Koskinen, 2012). The *APOE* ε4 allele was found to be correlated with longer duration of delirium in mechanically ventilated critically ill patients (Ely et al., 2007). There might be a connection between neurodegeneration due to pro-inflammatory response and enhanced *APOE* activity that causes cholinergic deficiency in POD patients. Even so, some studies question the association of *APOE* ε4 with delirium (Adamis et al., 2009; Bryson et al., 2011; Abelha et al., 2012).

Elevated serum cortisol levels were correlated with POD risk and degree, being dependent on hypothalamic-pituitary-adrenal axis hyperactivity at preexisting cognitive and functional impairment (van Munster et al., 2010a; Bisschop et al., 2011; Cerejeira et al., 2013; Colkesen et al., 2013; Kazmierski et al., 2013). A possible epigenetic explanation of cortisol sensitivity is the methylation of the glucocorticoid receptor gene *NR3C1* (nuclear receptor family 3, group C, member 1; Perroud et al., 2011). The increased diurnal cortisol and higher sensitivity to glucocorticoids were associated with homozygous *NR3C1* haplotype 4 (Manenschijn et al., 2011). The carriers of this haplotype had a 92% decreased risk of developing POD independently of age, cognitive and functional state (Manenschijn et al., 2011). This study concluded that development of delirium and its pathogenesis is correlated with glucocorticoid signaling. High levels of glucocorticoids affect working memory and thereby explain the cognitive deficits and inattention (Lupien et al., 1999). Mild cognitive impairment was further associated with increased cortisol levels and POD risk (Kazmierski et al., 2014b).

The neurometabolic pathway facilitates communication between brain and metabolic organs and consequently influences various neurodegenerative disorders, normal and pathophysiological aging (Siddiqui et al., 2012). Alteration in the neurometabolic status of the hippocampus can potentially impair growth and survival of neuronal cells, which is a common neuropathology of Alzheimer's disease (Wenk, 2003; Cong et al., 2013). Metabolic syndrome (e.g., hyperglycemia, diabetes) together with inflammation can contribute to cognitive decline (Yaffe et al., 2004). Prevention of metabolic syndrome by preoperative conventional glucose control might reduce the incidence of POD/POCD (Yaffe et al., 2004; Finfer et al., 2009).

The changes of amino acid concentrations in serum and urine have been associated with POD pathogenesis. An increased risk of delirium development was associated with decreased plasma tryptophan and the ratio of tryptophan as well as the increased or decreased ratio of tyrosine to large neutral amino acids (van der Mast et al., 2000; Robinson et al., 2008; Pandharipande et al., 2009). It was hypothesized that high levels of tyrosine lead to dopamine and norepinephrine excess that are involved in delirium pathogenesis (Pandharipande et al., 2009).

The low tryptophan levels might be associated with delirium via decreased synthesis of brain serotonin (van der Mast et al., 2000; Robinson et al., 2008; Pandharipande et al., 2009). de Jonghe et al. (2012) questioned the association between lower levels of tryptophan and delirium. Following the inflammatory response, tryptophan catabolisation via the kynurenine pathway is increased (Adams Wilson et al., 2012). Elevated plasma kynurenine and kynurenine/tryptophan ratio were correlated with fewer days without acute brain dysfunction in form of delirium or coma (Adams Wilson et al., 2012). Another suggested connection of tryptophan with delirium is alteration of melatonin production via serotonin synthesis (Pandharipande et al., 2009). Melatonin participates in regulation of circadian rhythms and quality and duration of sleep (Brzezinski, 1997). POD patients frequently have disrupted sleep-wake cycle, decreased delta melatonin concentrations (Yoshitaka et al., 2013) and abnormal circadian postoperative patterns of melatonin secretion (Shigeta et al., 2001).

Sunwoo et al. (2013) observed a higher frequency of normal and phosphorylated α-synuclein-positive pathologies in 16 delirious patients that underwent gastrostomy for stomach cancer. Sunwoo and colleagues concluded that POD clinical characteristics are analogous to the core features of α- as dementia with Lewy bodies, Parkinson disease dementia; patients experience altered sleep-wake cycles, visual hallucinations, disorganized thinking and attention impairment (Sunwoo et al., 2013). α-synuclein may be involved in the neurotransmitter release controlling through the SNARE complex (Kang et al., 1987; Tanzi et al., 1987). The delirious state is strongly influenced by the balance between cholinergic and dopaminergic systems, pro-inflammatory signaling, apolipoprotein E isoform, glucocorticoid signaling and the neurometabolic state. Many additional contributors at genetic, proteomic, metabolic and immune levels are to be expected.

Common Biomarkers of Postoperative Delirium and Cognitive Dysfunction

Postoperative delirium correlates with early postoperative cognitive dysfunction (at 7 days; Rudolph et al., 2008a; Hudetz et al., 2009) and delirious patients have 14 times greater chance of POCD development (Hudetz et al., 2009). In this chapter, we will discuss the common biomarkers found in both cognitive impairments, which are summarized in **Figure 2**.

Among the above-discussed genetic markers, the *APOE* ε4 allele was associated with greater risk to develop postoperative delirium (Adamis et al., 2007; Leung et al., 2007; van Munster et al., 2009a) and cognitive dysfunction at 7 days postoperatively (Cao et al., 2014). The association with POCD was however not detected by other studies of APOE ε4 variation at 1 week, 1–3 months and 1 year postoperatively (Abildstrom et al., 2004; Rentowl and Hanning, 2004; McDonagh et al., 2010; Bryson et al., 2011; Cao et al., 2014).

The elevated cortisol levels were detected in both POD (van den Boogaard et al., 2011; Cerejeira et al., 2013) and POCD patients (Zhang et al., 2014a). The magnitude of cortisol elevation correlated with levels of anti-inflammatory cytokine IL-10 and pro-inflammatory cytokine IL-6. Similarly to POD, POCD is associated with elevation of other pro-inflammatory markers including IL-1β, IL-8 and TNF-α (Rothenburger et al., 2001; Hudetz et al., 2011; Li et al., 2012; Bi et al., 2014). TNF-α stimulates IL-1β production in the brain and causes postoperative cognitive decline via peripheral cytokine cascade (Terrando et al., 2010). Reducing IL-1 release by peripheral TNF-α blockade might prevent POD, POCD and neuroinflammation (Terrando et al., 2010). Nonspecific acute-phase response in inflammation is present during POD and POCD. POCD patients have elevated levels of CRP following coronary artery bypass grafting (Hudetz et al., 2011), liver transplantation (Li et al., 2013b) and lumbar discectomy (Zhang et al., 2014a). Contradictory to previous findings, plasma levels of inflammatory marker matrix metalloproteinase-9 were decreased in POD patients and elevated in POCD patients (Girard et al., 2012; Zhang et al., 2014a).

Elevated levels of S100B were associated with POD (Pfister et al., 2008; van Munster et al., 2009b, 2010a,c; van den Boogaard et al., 2011). Likewise, POCD patients have increased serum levels of S100B, which is an indicator of neuronal injury (Rasmussen et al., 2000; Li et al., 2012; Lili et al., 2013). S100B-induced neuroinflammation mediates the RAGE (receptor for advanced glycation end product) signaling in microglia (Bianchi et al., 2007). The RAGE signaling pathway may up-regulate pro-inflammatory cytokines via NF-kappaB signaling, indicating its possible role in surgery-induced cognitive decline pathogenesis (Li et al., 2013a). Yet McDonagh et al. (2010) did not find an association between POCD and S100B or CRP.

BDNF showed correlation with POD occurrence in patients (Grandi et al., 2011) and POCD occurrence in aged mice (Tian et al., 2015). It was associated with other neuropsychiatric disorders such as schizophrenia, depression, bipolar disorder and has been suggested as early marker of brain injury (Chiaretti et al., 2003; Muglia et al., 2003; Teixeira et al., 2010).

Copeptin is correlated with severity of the illness and is presumed to be a prognostic measure of outcome prediction in acute illness (Katan and Christ-Crain, 2010). Postoperative plasma copeptin level can be an independent predictor of POD and POCD after coronary artery bypass graft surgery (Dixson et al., 2014). This study observed higher levels of postoperative copeptin in POD and POCD patients compared to controls.

A significant fluctuation of urinary 6-sulfatoxymelatonin (6-SMT), a major metabolite of melatonin, was detected in POCD patients compared to controls (Wu et al., 2014). Clinical subtypes of POD are differently related to the urinary levels of 6-sulfatoxymelatonin: hypoactive patients have higher 6-SMT, whenever hyperactive patients have lower 6-SMT (Balan et al., 2003). However, the association between melatonin and delirium has been challenged by independent studies after failure to confirm these findings (de Jonghe et al., 2014).

As mentioned above, postoperative delirium and cognitive dysfunction may have common contributing factors and biomarkers such as apolipoprotein E isoforms, cortisol signaling, pro-inflammatory cytokines, neurodegenerative marker S100B, copeptin and 6-sulfatoxymelatonin levels.

Biological Markers of Postoperative Cognitive Dysfunction

Patients with postoperative cognitive dysfunction display biomarkers distinct from delirious patients, which might be related not only to pathology but also postoperative time. The majority of the detected POCD biomarkers are related to inflammation. A recent study reported a positive association between the pro-inflammatory protein S100A8 and POCD development (Lu et al., 2015) and imbalance between T helper 17 cells, a pro-inflammatory subset of $CD4^+$T cells, and regulatory T cells, an anti-inflammatory subset of $CD4^+$T cells, was observed in POCD patients (Tian et al., 2015).

Postoperative cognitive dysfunction can be predicted by lower preoperative endotoxin immunity following cardiac surgery (Mathew et al., 2003). Lower preoperative levels of immunoglobulin M (anti-endotoxin core antibody) are associated with the greater incidence and severity of POCD (Mathew et al., 2003). A similar study by Rothenburger et al. (2001) suggested an association between lower levels of immunoglobulin M and elevated levels of endotoxin together with IL-8 (Rothenburger et al., 2001).

5′ adenosine monophosphate-activated protein kinase (AMPK) protects CNS by inhibition of inflammatory responses through various mechanisms, including NF-kappaB pathway (Sag et al., 2008; Salminen et al., 2011). This pathways includes NF-kappaB activation by chemokines, cytokines or adhesion molecules and activation of inflammatory cytokines IL-1 and TNF-α (Renard et al., 1997; Chandel et al., 2000). A significant elevation of NF-kappaB, IL-1β and AMPK was shown to result in Toll-like receptor 4 signaling on microglia in the hypothalamus of a POCD rat model (Wang et al., 2013; Bi et al., 2014). Interleukin-1β and NF-kappaB levels gradually decreased over postoperative days (Wang et al., 2013; Bi et al., 2014). Interleukin-1β can be a viable target to interrupt the POCD pathogenesis, as IL-1β-mediated inflammation was triggered by peripheral surgery-induced innate immune response (Cibelli et al., 2010). Another study demonstrated experimentally that inhibition of IL-1 receptors prevents development of POCD and neuroinflammation (Barrientos et al., 2012).

Le et al. (2014) suggested that hippocampus impairment leads to POCD development after they observed a significant reduction of neuronal dendritic spines and neuroinflammation signified by activated microglia, elevation of TNF-α and interleukin-1β in the hippocampi of aged rats. Amyloid beta 1–42 oligomers can impair cognitive and metabolic processes in the hippocampus (Pearson-Leary and McNay, 2012). The elevated levels of amyloid beta 1–42 were associated with a cognitive impairment caused by its interference with insulin signaling in the hippocampus (Pearson-Leary and McNay, 2012). The amyloid hypothesis suggests that amyloid beta peptide is deposited in the brain of Alzheimer's dementia patients and can form the senile plaques that perturb various signaling mechanisms (Cras et al., 1991). Old mice that developed short-term POCD upon abdominal surgery had Alzheimer's dementia-like changes: gliosis in brain, enhanced transcriptional and translational activity of the β-amyloid precursor protein, enhanced production of amyloid beta peptide, and hyper-phosphorylation of *tau* in the hippocampus (Wan et al., 2010). POCD patients after liver transplantation had significantly elevated levels of serum amyloid beta peptide, suggesting similar mechanisms as in Alzheimer's disease (Li et al., 2013b).

Urinary biomarkers could be promising diagnostic and prognostic indicators of postoperative cognitive dysfunction. A high ratio of trypsin inhibitor/creatinine was suggested to be an independent risk factor of POCD in lumbar discectomy patients (Zhang et al., 2014a). Urinary excretion levels of 8-isoprostane/creatinine were elevated as well in POCD patients at 7 days postoperatively compared to control patients (Cheng et al., 2013).

The major POCD biomarkers include inflammation-related molecules, imbalance between pro- and anti-inflammatory signaling and metabolic levels in urine.

Potential Biomarkers of Postoperative Delirium and Cognitive Dysfunction

At present, there is no standard biomarker for diagnosis and prognosis of postoperative cognitive impairments. Some findings on biomarker association with POD/POCD are contradictory. Thus, generation of genomic, proteomic and metabolomics data as well as implementation of imaging techniques such as MRI are required. In this section, we review the potential biomarkers possibly involved in occurrence and/or progression of postoperative delirium and cognitive dysfunction.

S100A8 (myeloid-related protein-8, calgranulin A), S100A9 (myeloid-related protein-14, calgranulin B), S100A12 (EN-RAGE, calgranulin C) are reliable markers of inflammation (Foell et al., 2004) and potential markers of plaque instability (Abbas et al., 2012). Inhibition of S100A9 significantly improved learning and memory, and reduced neuropathology of

Alzheimer's disease (Chang et al., 2012). Thus, it is promising to investigate potential connection between the calgranulins and POD/POCD.

As mentioned above, inflammation is associated with both POD and POCD. The pro-inflammatory cytokine IL-18 was not studied yet in the context of POD/POCD. Alzheimer's patients have increased levels of IL-18 in different regions of the brain (Ojala et al., 2009). Being co-localized with *tau*-protein and amyloid beta plaques, IL-18 mediates the hyperphosphorylation of *tau* (Ojala et al., 2009; Sutinen et al., 2012). IL-18 can influence the integrity of neurons and increase neuroinflammation in the brain (Bossù et al., 2010; Sutinen et al., 2012), thus contributing to cognitive decline in Alzheimer's disease (Bossù et al., 2008). IL-18 receptor complex (IL-18Rα/β) expression is perturbed in preclinical state of mild cognitive impairment and Alzheimer's disease (Salani et al., 2013). Specifically, IL-18Rα might play role in autoimmune brain damage (e.g., encephalomyelitis) via production of IL-17-producing T helper cells (Gutcher et al., 2006). A splice variant of IL-18Rβ encodes a putative truncated soluble protein that might be a regulator of IL-18 functioning (Andre et al., 2003).

SIGIRR (also called TIR8) is a potential inhibitor of pro-inflammatory IL-18, IL-1 and Toll-like receptor signaling (Thomassen et al., 1999; Wald et al., 2003; Mantovani et al., 2004). The anti-inflammatory effect of SIGIRR might be extended to the brain, as it inhibits inflammation in cooperation with IL-1F5 (a potential anti-inflammatory cytokine; Costelloe et al., 2008). TIGIRR receptor might be an accessory chain for mature IL-37a (Boraschi et al., 2011). IL-37a isoform is exclusively located in the brain and might be a potential anti-inflammatory cytokine (Boraschi et al., 2011). Another isoforms of IL-37 can bind to IL-18Rα and IL-18-binding protein, enhancing IL-18 inhibition (Boraschi et al., 2011).

IL1RAPL (IL-1 receptor accessory protein-like) gene was identified as a X-linked mental retardation locus (Carrié et al., 1999). *IL1RAPL* gene encodes a protein homologous to the IL-1/Toll receptor family. Patients with cognitive impairment had a nonsense mutation and deletions in *IL1RAPL* gene (Carrié et al., 1999). *IL1RAPL* gene might have a potential role in memory and learning functioning due to its over-expression in brain structures responsible for memory development such as hippocampus, dentate gyrus and entorhinal cortex (Carrié et al., 1999).

Several studies have reported a possible disruption of the blood-brain barrier integrity during POD (Pfister et al., 2008; Rudolph et al., 2008b). Blood-brain barrier disruption is associated with cognitive, behavioral and mood disturbances (Shalev et al., 2009). Zonulin is a protein that modulates the intercellular tight junction integrity and increases blood-brain barrier permeability (Fasano et al., 2000). Zonulin is involved in movement of macromolecules, fluid and leukocytes between intestinal lumen and bloodstream (Lu et al., 2000; Fasano, 2011). Since zonulin can increase intestinal and bovine brain microvessel endothelial cells permeability, the elevated circulating levels of zonulin can indicate blood-brain barrier pathologies (Karyekar et al., 2003; Fasano, 2011). Zonulin has been already associated with several diseases: celiac disease (Fasano et al., 2000; Fasano, 2011), schizophrenia (Wan et al., 2007), Devic's disease (Bai et al., 2009), multiple sclerosis (Takeoka et al., 1983) and Guillain-Barré syndrome (Jin et al., 2007; Yang et al., 2008).

Cholinergic-nicotinic genes can be implicated in POD/POCD pathology. Genetic variation within exon 5 of the α4 subunit of nicotinic acetylcholine receptor (*CHRNA4*) gene can modulate the attention network function (Winterer et al., 2007) and was implicated in nicotine dependence (Feng et al., 2004; Li et al., 2005). Several rare *CHRNA4* SNPs were negatively associated with nicotine dependence indicating its protective effect (Wessel et al., 2010; Xie et al., 2011). Nicotine can improve attention, memory and efficiently treat cognitive impairments (Rezvani and Levin, 2001). Patients with genetic variation of *CHRNA4* might abuse nicotine as self-medication of attention deficits in autosomal dominant nocturnal frontal lobe epilepsy (Hirose et al., 1999; Cho et al., 2003), schizophrenia (Winterer et al., 2007; Winterer, 2010) and attention deficit/hyperactivity disorder (Lambert and Hartsough, 1998). In addition, variants on the *CHRNA5-CHRNA3-CHRNA4* gene cluster, implicated in nicotine dependence, are associated with cognitive performance (Winterer et al., 2010).

System Biology Approaches for Biomarker Discovery

To identify, prevent or treat postoperative delirium and cognitive dysfunction we need to connect the incidental findings into an encompassing model and relate the pathomechanisms underlying POD/POCD with clinical outcomes. The biomarkers discussed so far are conceptually linked by the known molecular interactions and pathways and illustrated in **Figure 3.** Many findings are contradictory between cohorts and studies, which further complicates the investigation of underlying mechanisms. The toolbox of integrated systems biology can help to model the complex dependencies and conceptualize the unknown pathomechanisms contributing to POD/POCD origin and progression. Due to the sparse knowledge on cognitive impairments, we are limited in the choice of methodologies. Predictions of novel targets for study cannot utilize the simulations as appropriately large training and test data needs yet to be collected.

Knowledge maps formed by an integration of large-scale experimental data and text-mining results enable specialists to collaborate on highly detailed information. The dissection of the knowledge map into functionally/pathway enriched modules can reduce the overall complexity and indicate the sub-network(s) deregulated in POD/POCD. Networks built on the list of the seed genes/proteins reviewed in this article may indicate enriched pathways that are related directly or indirectly to POD/POCD. We can proceed with prediction of the upstream regulators, hubs and bottlenecks of the given pathways and sub-networks. Such regulators are potentially interesting as targets since they could modulate the network state and dampen imbalance and deregulation. Network approach enables us to study dynamical changes of the system such as

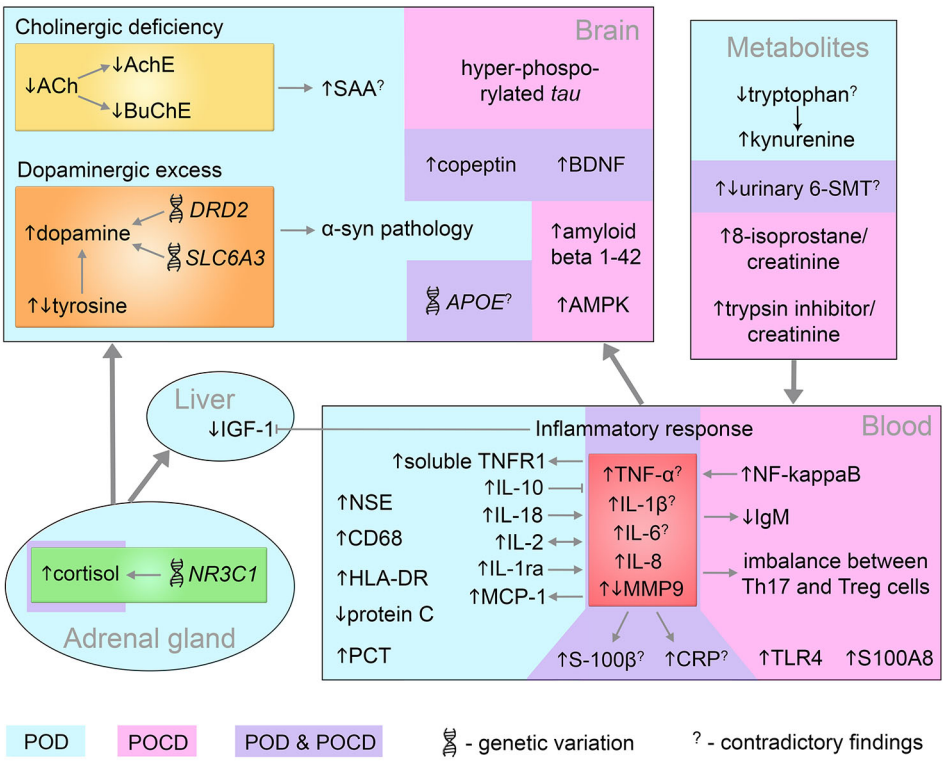

FIGURE 3 | Systems-level interaction of POD and POCD biomarkers. Biomarkers identified in POD and POCD patients are in blue and pink area respectively. The common POD/POCD biomarkers are presented in the violet area. 6-SMT, 6-sulfatoxymelatonin; ACh, acetylcholine; AchE, acetylcholinesterase; AMPK, 5′ adenosine monophosphate-activated protein kinase; *APOE*, apolipoprotein E; BDNF, brain-derived neurotrophic factor; BuChE, butyrylcholinesterase; CD68, cluster of differentiation 68; CRP, C-reactive protein; *DRD2*, dopamine receptor D2; HLA-DR, human leukocyte antigen-DR; IGF-1, insulin growth factor-1; IgM, immunoglobulin M; IL, interleukin; MCP-1, monocyte chemotactic protein 1; MMP9, matrix metalloproteinase-9; NF-kappaB, nuclear factor kappa B; *NR3C1*, nuclear receptor family 3, group C, member 1; NSE, neuron specific enolase; PCT, procalcitonin; S100A8, S100 calcium binding protein A8 (myeloid-related protein-8, calgranulin A); S100B, S100 calcium binding protein B; SAA, serum anticholinergic activity; *SLC6A3*, solute carrier family 6, member 3; Th17, T helper 17 cells; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor-1; Treg, regulatory T cells; α-syn, alpha-synuclein.

responsiveness, adaptation and stability. For example, network analysis of the metabolic positron emission tomography scans from Parkinson's disease patients identified two distinct disease-related patterns (Eckert et al., 2007). One of the patterns is related to motor manifestations of Parkinson's disease, the other pattern is correlated with the patients' performance on memory and executive functioning tests. In case of POD/POCD, networks can initially be based on the literature mining results where large-scale human experimental data is not accessible. Networks based on experimental data and supported by literature evidence may give stronger results and reflect the network dynamics.

Systems biology methods, applied to Parkinson's disease, made a significant contribution for integration of known pathomechanisms. Parkinson's disease is a multi-factorial condition with complex interplay between genetic and environmental factors (Calne et al., 1986). A recently published Parkinson's disease map is able to capture the known contributing mechanisms, integrate the underlying pathways and visualize large experimental data on top of the solid, literature derived and reviewed network (Fujita et al., 2014). The principle of the Parkinson's disease map could be well applied to investigate other complex diseases including POD and POCD.

Magnetic resonance imaging revealed the vulnerable regions in brain of POD patients (Root et al., 2013) as well as white-matter hyperintensities (Hatano et al., 2013) and brain atrophy (Gunther et al., 2012). Integration of imaging results with information at different levels (i.e., DNA, RNA, proteins, etc.) gives a rise to mathematical/computational modeling of POD and POCD states. Iterative prediction and cross-validation steps improve such models and system behavior and response to perturbations can be predicted. For instance, neuroimaging integration with genetic and demographic information by a Support Vector Machine algorithm successfully differentiated Alzheimer disease and mild cognitive impairment from controls (Kohannim et al., 2010). The integrated systems biology approaches in the context of POD/POCD lead a step forward to personalized medicine and effective clinical trials.

Conclusion

Postoperative delirium and cognitive dysfunction has been elucidated on the molecular basis and many biomarkers have been identified. Hypotheses to explain the major features of the disease onset and pathology were formulated but at this point, we understand little how much the markers and mechanisms explain the pathology. In particular, we know little about possible molecular influences on POD/POCD sub-types such as slow and fast progression or hypo- and hyperactive delirium. Common molecular mechanisms with other syndromes, in particular schizophrenia, promise further insights but have not been investigated on a sufficient scale. As neuropsychiatric syndromes present themselves in the most complex manner, we require global standardization efforts and patient cohorts for comparative investigations.

We have reviewed the knowledge about molecular mechanisms underlying POD and POCD and described many biomarkers associated with these postoperative complications, and it is clear that postoperative delirium and cognitive dysfunction are multifactorial conditions. Among the identified pathomechanisms, some biomarkers were common, such as elevation of TNF-α, interleukin-1β, interleukin-6, interleukin-8, interleukin-10, CRP, S100B, matrix metalloproteinase-9, BDNF, copeptin and cortisol levels as well as presence of ApoE ε4 allele. The application of integrated systems biology approaches may elucidate the unknown pathomechanisms contributing to POD/POCD origin and progression. Combining experimental measurements, imaging techniques and mathematical/computational modeling can give a potential to reconstruct the underlying network of molecular interactions and predict reliable biomarkers of postoperative delirium and cognitive dysfunction.

PubMed Search Strategy

We reviewed the pertinent literature retrieved by a search in the PubMed database (on November 20, 2014) using the following query: "(biomarker OR marker) AND [(postoperative delirium) OR delirium OR (postoperative cognitive dysfunction) OR POCD] AND (hasabstract[text] AND Humans[Mesh]) NOT (Alzheimer OR Parkinson)". The search yielded 254 publications. The ones cited in the review are those that, in the author's view, make a substantial contribution to the knowledge about existing and potential biomarkers of POD/POCD.

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Using the Chinese version of Memorial Delirium Assessment Scale to describe postoperative delirium after hip surgery

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Objective: Memorial Delirium Assessment Scale (MDAS) assesses severity of delirium. However, whether the MDAS can be used in a Chinese population is unknown. Moreover, the optimal postoperative MDAS cutoff point for describing postoperative delirium in Chinese remains largely to be determined. We therefore performed a pilot study to validate MDAS in the Chinese language and to determine the optimal postoperative MDAS cutoff point for delirium.

Methods: Eighty-two patients (80 ± 6 years, 21.9% male), who had hip surgery under general anesthesia, were enrolled. The Confusion Assessment Method (CAM) and Mini-Mental State Examination (MMSE) were administered to the patients before surgery. The CAM and MDAS were performed on the patients on the first, second and fourth postoperative days. The reliability and validity of the MDAS were determined. A receiver operating characteristic (ROC) curve was used to determine the optimal Chinese version MDAS cutoff point for the identification of delirium.

Results: The Chinese version of the MDAS had satisfactory internal consistency (α = 0.910). ROC analysis obtained an average optimal MDAS cutoff point of 7.5 in describing the CAM-defined postoperative delirium, with an area under the ROC of 0.990 (95% CI 0.977–1.000, $P < 0.001$).

Conclusions: The Chinese version of the MDAS had good reliability and validity. The patients whose postoperative Chinese version MDAS cutoff point score was 7.5 would likely have postoperative delirium. These results have established a system for a larger scale study in the future.

Keywords: memorial delirium assessment scale, confusion assessment method, postoperative delirium, hip surgery, Chinese

INTRODUCTION

Delirium is a disturbance of consciousness with an acute onset and a fluctuating nature, that is accompanied by changes in cognition or perceptual disturbances which are not attributable to pre-existing psychiatric disorders or substance-induced states (American-Psychiatric-Association, 1997). It has been suggested that surgery and anesthesia are associated with post-operative cognitive disorders including delirium (Kapila et al., 2014). It is estimated that delirium occurs in 14% to 56% of elderly patients following surgery under anesthesia, and postoperative delirium is one of the most common postoperative complications in older adults (Breitbart et al., 1997; DeCrane et al., 2011; Rudolph and Marcantonio, 2011; Marcantonio, 2012).

Postoperative delirium usually manifests itself as disorientation, cognitive impairment and alteration of mental processes; it can present itself either in a hyperactive form, a hypoactive form or a combination of these two forms (Field and Wall, 2013). Postoperative delirium has been reported to be associated with prolonged hospitalization, long-term

Abbreviations: MDAS, Memorial Delirium Assessment Scale; CAM, Confusion Assessment Method; MMSE, Mini Mental State Examination.

cognitive impairment, functional deficits, increased morbidity and mortality, as well as adding to the burdens of caregivers (Meagher et al., 2000; Leslie and Inouye, 2011; Saczynski et al., 2012). Although it significantly impacts patient recovery after surgery, postoperative delirium often goes unrecognized (Neufeld and Thomas, 2013). Hence, an effective assessment, using validated tools, is important for the purpose of identifying the severity and the overlooked incidences of postoperative delirium.

The Confusion Assessment Method (CAM; Inouye et al., 1990), which has been translated into Chinese (Leung et al., 2008), is widely used to determine the prevalence of delirium. The Memorial Delirium Assessment Scale (MDAS) has been used to assess the severity of delirium based on 10 features (Breitbart et al., 1997; Marcantonio et al., 2002).

The MDAS has been translated into multiple languages, utilized in different countries, and has good reliability and validity (Grassi et al., 2001; Matsuoka et al., 2001; Shyamsundar et al., 2009; Noguera et al., 2014). However, the MDAS has not been translated into Chinese, and it remains unknown whether it can be used to identify postoperative delirium and assess its severity in Chinese people. Therefore, we set out to perform a prospective investigation with 82 Chinese patients, who had hip surgery under general anesthesia, in Shanghai, P.R. China, to assess the validity and reliability of MDAS in a Chinese population. Moreover, we determined the optimal MDAS cutoff point for describing the postoperative delirium of the Chinese patients, defined by CAM. The primary objective was to determine whether the MDAS had good reliability and validity in the Chinese language. The secondary objective was to assess the extent to which there was an optimal postoperative cutoff point in the Chinese version of MDAS; the scores above this cutoff point would be strongly associated with the presence of delirium, as determined by the CAM diagnostic algorithm.

METHODS

PARTICIPANTS

The protocol was approved by the Human Research Ethics Committee of the Tenth People's Hospital in Shanghai, P. R. China [RES- 2013015]. A total of 130 patients, who had hip fractures and were admitted to the Department of Orthopedics in the Tenth People's Hospital, were screened and asked to participate in the study. Participants were included if they met the following eligibility criteria: (1) age 65 years or older; (2) patients who had hip replacements or open reductions with internal fixation (ORIF) under general anesthesia for the repair of hip fractures. Patients were excluded from participation if they had: (1) cognitive impairment at enrollment (MMSE scores less than 18); and/or (2) pre-existing delirium, cerebrovascular disorders or mental disorders (e.g., depression or schizophrenia), diagnosed by using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American-Psychiatric-Association, 1997). All participants signed the written informed consent before being enrolled in the study. The participants were screened for the study from August, 2013 to December, 2013. One hundred and thirty participants were enrolled and the data from 82 participants were included for the final data analysis (see the Flow diagram). Sample size was calculated by determining the difference in MDAS scores between the participants with delirium and the participants without delirium in our pilot study with 80% power and 5% type I error.

Pre-operative interview

Screening assessments were performed 1 day before the scheduled surgery and included demographic characteristics (e.g., age, gender and education), medical information (e.g., diagnosis and type of surgery), and evaluation of cognitive function using the Mini-Mental State Examination (MMSE). The CAM was also performed on the participants one day before the surgery.

Anesthesia and surgery

All of the participants had hip replacements or open reductions with internal fixation under general anesthesia for the repair of hip fractures. The participants had standardized perioperative care, including preoperative medication, general anesthesia, and postoperative pain control. The participants were given midazolam (1.6 ± 0.59 mg, intravenous administration) as preoperative medication. The general anesthesia was induced by intravenous administration of propofol (95.56 ± 42.51 mg), sufentanil (14.45 ± 6.51 μg), and cisatracurium (10.52 ± 4.51 mg). The general anesthesia was maintained by using propofol (295.66 ± 121.14 mg), remifentanil (0.89 ± 0.28 mg), sevoflurane (21.54 ± 6.78 ml), and cisatracurium (7.52 ± 3.45 mg). The postoperative pain control included a standard postoperative pain management, e.g., sufentanil and butorphanol patient-controlled analgesia (0.5 μg sufentanil and 0.0125 mg butorphanol per injection, interval time of injection was 15 min with a total of 2 μg sufentanil and 0.05 mg butorphanol per hour). There were no major complications among the participants during the immediate postoperative period.

Post-operative interview

The assessment of delirium was performed after surgery once per day between 8:00 am and 2:00 pm. Patient charts were not reviewed for episodes of delirium, which could have occurred outside the time of assessment. The prevalence of postoperative delirium was assessed by a psychiatrist, (Yujie Wu), according to the CAM diagnostic algorithm. The severity of delirium was determined with the MDAS by another psychiatrist, (Zhongyong Shi), who was blinded to the results of the CAM. The psychiatrists who performed the delirium assessments in the current study had good training and went through quality control procedures. In the current study, the CAM and MDAS were conducted on the first (day 1), second (day 2) and fourth (day 4) day after the surgery by these psychiatrists, because postoperative delirium occurs most often on postoperative day 1 and 2. We performed the CAM and MDAS on postoperative day 4 to detect late-occurring postoperative delirium cases.

Confusion Assessment Method (CAM). The CAM algorithm consists of four clinical criteria: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. For delirium to be defined, both the first and the second criteria have to be present, plus either: the third

or the fourth criteria present, or both the third and forth criteria present together (Inouye et al., 1990). The CAM in the Chinese language has been proven to have good reliability and validity with use in the Chinese elderly population (Leung et al., 2008).

Memorial Delirium Assessment Scale (MDAS). The original MDAS is designed to assess the severity of delirium symptoms, and it contains ten items: (1) awareness; (2) orientation; (3) short-term memory; (4) digit span; (5) attention capacity; (6) organizational thinking; (7) perceptual disturbance; (8) delusions; (9) psychomotor activity; and (10) sleep-wake cycle (Breitbart et al., 1997). Each item is rated from 0 (none) to 3 (severe) depending on the level of impairment. Translation and back-translation methods were used to create the Chinese version of the MDAS. The MDAS was first translated into Chinese by Yingbo Zhu and then back-translated into English by Zhongyong Shi. The original English version and the back-translated English version of the MDAS were compared, and the translation variations were inspected for consistency. All of the items with variances were then translated into Chinese and back-translated into English again according to suggestions from consistency discussions. The final Chinese version of the MDAS was generated only if its back-translated English version was consistent with the original English version of the MDAS.

Statistics

Participants' characteristics, including age, height, weight, education, length of anesthesia, length of operation, estimation of blood loss and MDAS and MMSE scores, were presented as means ± standard deviation (SD). Continuous parameters were compared with the Analysis of Variance (ANOVA) or Student *t*-test. Categorical factors, such as gender, were compared with the Chi-square test. All analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL) with $P < 0.05$ as the significance level.

Reliability. Reliability was determined by using Cronbach's alpha coefficient. The Cronbach's alpha coefficient was calculated to assess internal consistency between MDAS items (inter-item reliability).

Validity. Concurrent validity of the MDAS was evaluated by Student *t*-test, comparing the MDAS scores (average of day 1, 2 and 4 after surgery) between patients with or without delirium, as determined by the CAM. The hypothesis was that higher MDAS scores would be associated with the presence of CAM-defined delirium.

Determination of optimal MDAS cutoff point. A receiver operating characteristic (ROC) curve was used to determine the optimal MDAS cutoff point for description of CAM-defined postoperative delirium. The total area under the curve (AUC), its 95 % confidence interval (CI), the total accuracy and the Kappa value, were all used for this determination. The optimal MDAS score was calculated as: (maximum of [sensitivity + specificity − 1]).

RESULTS

CHARACTERISTICS OF PARTICIPANTS

One hundred and thirty patients were initially screened, and a total of 82 patients were included in the final data analysis (see **Figure 1**, the flow diagram). The demographic and clinical data of the participants are presented in **Table 1**. All of the participants had hip replacement ($N = 43$) or ORIF ($N = 38$) surgeries. Twenty-one of the 82 participants (25.6%) developed postoperative delirium either on day 1, day 2 or day 4. The prevalence of delirium in this patient population on day 1, day 2 and day 4 were 17 (20.7%), 17 (20.7%) and 13 (15.8%), respectively.

RELIABILITY AND VALIDITY OF MDAS

The overall Cronbach's alpha of the Chinese MDAS was 0.910. **Table 2** shows the values of alpha for the MDAS in Chinese when a given item is removed. There was no single item that might affect the scale (alpha range between 0.899 and 0.913). The column "Item Total *r*" indicates the correlation between individual items and total MDAS scores. Defined by "Item-total *r*", most items (1, 2, 3, 4, 5, 6, 7, 8 and 9) showed strong ($r \geq 0.7$) or moderate ($0.5 \leq r < 0.7$) correlation with the MDAS total score. Item 10 had a weak correlation with the total MDAS score ($r < 0.5$) (**Table 2**). These data point to the good internal consistency (reliability) of the MDAS.

Moreover, the participants who developed postoperative delirium had a higher MDAS score (average of day 1, 2 and 4 after surgery) than the participants who did not develop postoperative delirium: 11.44 ± 4.81 vs. 3.14 ± 1.81 ($P < 0.0001$, Student *t*-test).

THE OPTIMAL CHINESE VERSION MDAS CUTOFF POINT IN DESCRIBING POSTOPERATIVE DELIRIUM

ROC analysis was performed to determine the optimal MDAS cutoff point, which combined the CAM-defined postoperative

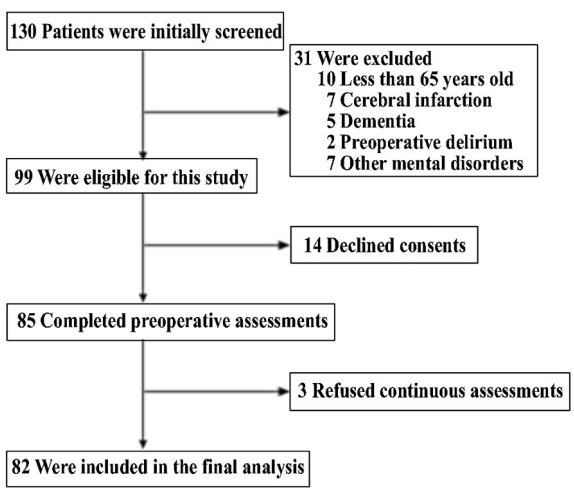

FIGURE 1 | Flow diagram. The diagram shows that 130 participants were initially screened for the studies and 82 participants were included in the final data analysis.

Table 1 | Demographic and clinical characteristics of the study population.

Variables	Value
Age (years)	
Mean ± SD	80.24 ± 6.00
Less than 75	15 (18.8%)
76–80	22 (27.5%)
81–85	32 (40.0%)
More than 86	11 (13.8%)
Gender, male (%)	18 (21.9%)
Marital status, married	78 (94.7%)
Height (cm) mean ± SD	155.00 ± 8.60
Weight (kg) mean ± SD	54.30 ± 9.13
BMI (kg/m^2)	25.17 ± 3.25
Education (years) mean ± SD	4.20 ± 4.81
Disease, hip fracture	82 (100%)
Anesthesia, general anesthesia	82 (100%)
ASA class	
I	2 (2.6%)
II	51 (63.8%)
III	25 (31.3%)
Unknown	2 (2.5%)
Length of anesthesia (minutes) mean ± SD	127.09 ± 43.63
Length of operation (minutes) mean ± SD	91.66 ± 40.44
Estimated blood loss (mL) mean ± SD	314.49 ± 263.33
MMSE (points) mean ± SD	21.68 ± 5.28

Abbreviation: ASA, American Society of Anesthesiologists; BDS, Blessed Dementia Scale; ADL, Activities of Daily Living; MMSE, Mini-Mental State Examination; SD, standard deviation; cm, centimeter; min, minute; kg, kilogram; mL, milliliter.

delirium assessments of days 1, 2 and 4. The area under the ROC curve was 0.990 (95% CI 0.977-1.000, $P < 0.001$) (**Figure 2**). An optimal MDAS cutoff point of 7.5, (combining the CAM-defined postoperative delirium assessments of days 1, 2 and 4), was obtained by Youden index (maximum of [sensitivity + specificity − 1]). Employing this defined cutoff point for the MDAS score, 45 out of 47 patients were identified as having delirium (defined by the CAM from days 1, 2 and 4), and two other patients were identified as not having delirium. The sensitivity of these identifications was 95.7%. Among the 199 patients without delirium (defined by the CAM from days 1, 2 and 4), 195 of them were identified as not having delirium and only four were identified as having delirium using this MDAS value (7.5). The specificity of the identification was 98.0%. Total identification accuracy of the MDAS vs. the CAM was 97.6%, and the Kappa value for concordance between the MDAS (using the cutoff value of 7.5) and the CAM, was 0.922 (Kappa statistic, $P < 0.001$). The positive and negative predictive values of this MDAS score (7.5) were 0.918 and 0.990, respectively (**Table 3**).

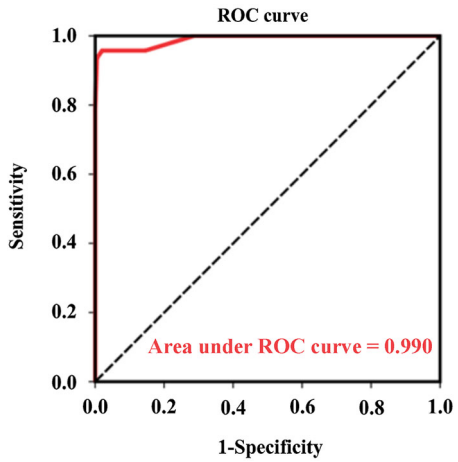

FIGURE 2 | Receiver operating characteristics (ROC) analysis was used for determination of the diagnostic sensitivity and specificity of the optimum value of the MDAS score vs. the CAM. The area under the curve (AUC) is 0.990 (95% CI: 0.977–1.000, $P < 0.001$). Optimal cutoff point for MDAS is 7.5, at which point a sensitivity of 0.905 and a specificity of 0.984 are achieved. CI, confidence interval.

Table 2 | Reliability and validity of Chinese version of MDAS.

MDAS	Inter-item reliability	
Item	α if item removed	Item-total *r*
1	0.899	0.731**
2	0.905	0.858**
3	0.907	0.760**
4	0.907	0.769**
5	0.892	0.701**
6	0.892	0.760**
7	0.902	0.642**
8	0.903	0.580**
9	0.890	0.730**
10	0.913	0.343**
Total	—	0.910**

Abbreviation: MDAS, Memorial Delirium Assessment Scale; CAM, confusion assessment method.

Note: Item-total and total-total r-values were based on Spearman rank-order correlation.

***Correlation is significant at the 0.01 level (2-tailed).*

DISCUSSION

In this prospective clinical study, we aimed to validate the MDAS with a Chinese population, and to determine the optimal MDAS cutoff point in identifying delirium with 82 Chinese patients who had hip surgery under general anesthesia. First, we found that the Chinese version of the MDAS has good reliability and validity.

Table 3 | The sensitivity and specificity of optimal MDAS score in describing the CAM-defined postoperative delirium.

Tests		CAM		Positive/Negative predictive values	Sensitivity/ Specificity
		Delirium	Non-delirium		
MDAS	Positive	45 (18%)	4 (2%)	0.918/0.990	0.957/0.980
	Negative	2 (1%)	195 (79%)		

The optimal MDAS score was obtained by merging MDAS scores of postoperative days 1, 2 and 4. Among 47 patients, who were diagnosed with delirium according to the CAM, 45 of them were defined as having delirium by the MDAS using the cutoff score of 7.5. The positive predictive value is 0.918, the diagnostic sensitivity of the MDAS is 0.957, and the specificity is 0.980.

The data suggest that MDAS can be used in a Chinese population. Additionally, we found that a Chinese version MDAS score of 7.5, averaged from postoperative day 1, 2 and 4 scores, could be an optimal value for describing CAM-defined postoperative delirium in the patients who had hip surgeries under general anesthesia.

Previous studies have reported the prevalence of postoperative delirium in patients who had hip surgery for the repair of hip fractures as varying between 22.2% and 62.0% (Marcantonio et al., 2000, 2001; Gruber-Baldini et al., 2013; Bellelli et al., 2014; Brown et al., 2014; Holly et al., 2014). The postoperative delirium prevalence in the current study was 25.6% for the patients who had hip surgery, a similar value to one obtained in another study (Brown et al., 2014). The current study aimed to test the usefulness of the MDAS in postoperative delirium studies. We were able to find a significant difference in the MDAS scores of patients with postoperative delirium and patients without postoperative delirium, thus highlighting the effectiveness of the MDAS in identifying the presence and severity of delirium cases. Furthermore, the establishment of the current system will enable us to use the Chinese version of the MDAS to further assess the severity of delirium in the Chinese population in the future.

The MDAS has demonstrated good reliability and validity in clinical applications, and has retained its psychometric characteristics in different languages (Grassi et al., 2001; Matsuoka et al., 2001; Shyamsundar et al., 2009; Noguera et al., 2014). The current findings show that the MDAS in the Chinese language also had good internal consistency. Additionally, the MDAS in Chinese demonstrated a high degree of concurrent validity compared with the CAM (**Table 3**). As a result, these findings have established a system which will allow a larger scale study using both the CAM and the MDAS to be carried out in a future Chinese population.

The MDAS has been suggested to not only assess the severity of symptoms of delirium, but also to identify delirium, in previous studies. Specifically, Breitbart et al. reported that an MDAS score of 13 was an optimal value in identifying postoperative delirium in acquired immunodeficiency syndrome (AIDS) patients (Breitbart et al., 1997). Lawler et al. suggested an optimal MDAS score of 7, in another MDAS validation study, for cancer patients (Lawlor et al., 2000). Similarly, in the current study, an optimal MDAS cutoff point of 7.5 was obtained by ROC analysis based on the combined prevalence of delirium on postoperative day 1, day 2 and day 4. The optimal MDAS cutoff point of 7.5 identified most of the delirium patients determined by the CAM. These findings suggest that the Chinese version MDAS cutoff point of 7.5 offers optimal potential for determining the presence or absence of delirium; specifically, patients who had a MDAS score of 7.5, likely had delirium after hip surgery under general anesthesia.

The ROC result was close to ideal for the current study. These ideal findings are likely due to the fact that dementia patients were excluded from the cohort. The inclusion of participants with dementia would have led to less ideal ROC results, because participants with dementia would likely get higher MDAS scores even without delirium (Marcantonio et al., 2002).

We used the MMSE score of 18 as the cutoff value in defining cognitive impairment in the current study, as suggested in a previous study in a Chinese population (Katzman et al., 1998). The Chinese version of the MMSE, which includes five aspects (orientation, short-term memory, attention and calculation, language, and visuospatial), has demonstrated good reliability and validity among older Chinese adults (Katzman et al., 1998). The cutoff MMSE score in defining cognitive impairment is relatively lower in the Chinese population due to educational and cultural differences, which have been reported in previous studies (Zhang et al., 1990; Katzman et al., 1998; Sahadevan et al., 2001). Note that this MMSE cutoff score in identifying cognitive impairment has been accepted and is often utilized in studies in the Chinese population (Li et al., 2003; Zhou et al., 2006).

There are 10 items in the MDAS (Breitbart et al., 1997). The tenth item is the sleep-wake cycle. Interestingly, the tenth item demonstrated a weak correlation with the total MDAS score in the current study ($r < 0.5$) (**Table 2**). These findings suggest that sleep disturbance is common in both the participants with delirium and the participants without delirium. Future studies may aim to determine whether the item of sleep-wake cycle could be removed from the MDAS.

There were several limitations in the current study. First, patients were assessed for delirium only on postoperative days 1, 2 and 4, but not on day 3 or on later days after the surgery (e.g., postoperative day 7). However, most cases of postoperative delirium occur in the first 2 days after surgery. In addition, we only included participants who had hip replacements or open reductions with internal fixation under general anesthesia for the repair of hip fractures in the current study. It is possible that patients who have different types of surgeries (e.g., cardiac surgery) may have different optimal MDAS scores for the purpose of identifying postoperative delirium. Future studies may need to include patients undergoing other kinds of surgeries.

In conclusion, the results from the current study show that the MDAS in the Chinese language could be an effective and reliable method for determining the severity of delirium symptoms in older Chinese adults. Moreover, a cutoff score of 7.5 was discovered to have a very strong agreement with the CAM algorithm and can therefore be used to diagnose delirium. The findings from this pilot study have established a system and have provided preliminary data for future, larger-scale research with a Chinese population on postoperative delirium determined by using both the CAM and the MDAS. With the establishment of this current system, we should be able to use the Chinese version of the MDAS in the future to assess the severity of postoperative delirium in different Chinese populations.

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Determinants of frailty: the added value of assessing medication

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This study aims to analyze which determinants predict frailty in general and each frailty domain (physical, psychological, and social), considering the integral conceptual model of frailty, and particularly to examine the contribution of medication in this prediction. A cross-sectional study was designed using a non-probabilistic sample of 252 community-dwelling elderly from three Portuguese cities. Frailty and determinants of frailty were assessed with the Tilburg Frailty Indicator. The amount and type of different daily-consumed medication were also examined. Hierarchical regression analysis were conducted. The mean age of the participants was 79.2 years (±7.3), and most of them were women (75.8%), widowed (55.6%) and with a low educational level (0–4 years: 63.9%). In this study, determinants explained 46% of the variance of total frailty, and 39.8, 25.3, and 27.7% of physical, psychological, and social frailty respectively. Age, gender, income, death of a loved one in the past year, lifestyle, satisfaction with living environment and self-reported comorbidity predicted total frailty, while each frailty domain was associated with a different set of determinants. The number of daily-consumed drugs was independently associated with physical frailty, and the consumption of medication for the cardiovascular system and for the blood and blood-forming organs explained part of the variance of total and physical frailty. The adverse effects of polymedication and its direct link with the level of comorbidities could explain the independent contribution of the amount of prescribed drugs to frailty prediction. On the other hand, findings in regard to medication type provide further evidence of the association of frailty with cardiovascular risk. In the present study, a significant part of frailty was predicted, and the different contributions of each determinant to frailty domains highlight the relevance of the integral model of frailty. The added value of a simple assessment of medication was considerable, and it should be taken into account for effective identification of frailty.

Keywords: elderly, frailty, determinants, comorbidity, medication

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Introduction

As age increases, physiological reserves inevitably decrease in multiple systems, and comorbidities become more prevalent (WHO, 1999). Nonetheless, chronological age is not a precise indicator of functional decline (Bergman et al., 2007). The changes that accompany aging depend on genetic

and environmental factors, and are lifestyle and life event related (WHO, 1999). Therefore, while some may remain healthy and resilient in later life, others may become increasingly vulnerable to internal and external stressors. The latter refers to a state of frailty.

Frail individuals are at greater risk of clinically significant adverse outcomes such as hospitalization, institutionalization and mortality (Fried et al., 2004, 2009; Abellan van Kan et al., 2008). Although frailty is generally considered a clinical syndrome separate from the normal aging process, there are different perspectives about its definition (Hogan et al., 2003; Markle-Reid and Browne, 2003; Bergman et al., 2007; Sternberg et al., 2011). More traditional approaches to the concept describe frailty as an exclusively physical condition (presence of three or more of the following components: weight loss, low physical activity, exhaustion, slowed performance, and weakness; Fried et al., 2001), or as a result of the accumulation of multidimensional deficits (e.g., disabilities, symptoms, signs, diseases; Rockwood and Mitnitski, 2007). On the other hand, following the more current trends of frailty definition, the recently described integral conceptual model specified frailty as a dynamic pre-disability state that includes losses in physical, psychological and/or social domains (Gobbens et al., 2010a,b,c).

A broader definition of frailty also involves that the factors considered as underlying a state of increased vulnerability are beyond the decline of physiological reserve and comorbidity. In fact, according to the integral conceptual model of frailty, life course determinants such as sociodemographic characteristics and lifestyle, life event and environment-related factors can directly influence frailty, besides influencing the onset of diseases which can also lead to frailty (Gobbens et al., 2010c,d, 2012). From this standpoint, as multiple circumstances may impact the onset of frailty in older persons, researchers should focus on ascertaining which elements are associated with frailty in different contexts.

This study's main objective was to analyze which determinants – described in the integral conceptual model of frailty – contribute to the prediction of frailty in general and of each frailty domain (physical, psychological, and social), in a sample of Portuguese community-dwelling individuals aged 65 years and over. Furthermore, the present study examined if a simple and objective measurement, such as assessing the number of daily-consumed medications, could help to explain frailty variance, after controlling for the effect of the determinants. It is hypothesized that a higher medication consumption is independently associated with increased frailty levels. In this context, the independent contribution of each type of daily-consumed drugs was also studied.

Materials and Methods

Study Design and Participants

A cross-sectional study was conducted with a non-probabilistic sample of 252 community-dwelling elderly (aged 65 years and over), in three northern Portuguese cities (Maia, Porto, and Vila Nova de Gaia).

Exclusion criteria were severe cognitive impairment (according to guidelines of the National Institute for Health and Care Excellence (NICE, 2011), participants with Mini Mental State Examination (Folstein et al., 1975) scores below 10 were excluded) and being unable to speak Portuguese.

Participants were interviewed in 16 local community institutions, such as social, recreation and day care centers, as well as senior universities. Trained researchers conducted the interviews from May to September 2013, using structured questionnaires. The study was approved by institutional review boards and by the ethics committee of the Ph.D. in Gerontology and Geriatrics (Institute of Biomedical Sciences Abel Salazar – University of Porto). All the participants gave their written informed consent before the interview.

Measurements

Frailty and determinants of frailty were assessed with the Tilburg Frailty Indicator (TFI; Gobbens et al., 2010e), which is an operationalization of the integral conceptual model of frailty. This brief self-report questionnaire comprises two subscales (parts A and B). Part A is composed of 10 questions about determinants of frailty: sociodemographic characteristics (age, sex, marital status, nationality, level of education, and income); life events in the last year (death of a loved one, serious illness, serious illness in a loved one, divorce or end of an important relationship, traffic accident, and crime); assessment of how healthy the respondent's lifestyle is; satisfaction with home living environment; and the presence of two or more chronic diseases. Part B measures frailty in three domains: physical (physical health, unexplained weight loss, difficulty in walking, difficulty in maintaining balance, hearing problems, vision problems, lack of strength in hands, and physical tiredness), psychological (cognition, depression and anxiety symptoms, and coping), and social (living alone, social relations and support). All items are rated dichotomously (0–1), with higher scores meaning higher frailty. Scores for each frailty domain and a total frailty score (0–15) are produced. The Portuguese version of TFI (Coelho et al., 2014) was used. This tool has a good internal consistency (KR-20 $= 0.78$) and test–retest reliability ($r = 0.91$) for total frailty score, and there is encouraging evidence regarding its construct and criterion validity (Coelho et al., 2014).

Medication was assessed in terms of the type and number of different daily-consumed drugs. In order to prevent recall bias, participants were previously asked to bring their medication or prescriptions to the interview. Based on the guidelines for ATC classification and DDD assignment (WHO, 2014), the following groups of medication were considered: cardiovascular system [e.g., diuretics and angiotensin-converting-enzyme (ACE) inhibitors], nervous system (e.g., psycholeptics and analgesics), metabolism (e.g., antidiabetics and mineral supplements), musculoskeletal system (e.g., anti-inflammatories and antirheumatics), digestive system (e.g., antacids and laxatives), blood and blood forming organs (e.g., antiplatelets and anticoagulants), respiratory system (e.g., bronchodilators and antihistamines), genitourinary system (e.g., antispasmodics and medicines for benign prostatic hyperplasia), endocrine system (e.g., corticosteroids and

drugs for thyroid-related diseases), and other clinical conditions (e.g., infections and diseases of the sensory system).

Finally, measures of cognitive [MMSE (Folstein et al., 1975)], functional [Barthel Index (Mahoney and Barthel, 1965)/Lawton and Brody Scale (Lawton and Brody, 1969)] and nutritional status [Body Mass Index (BMI)] were used for the descriptive analysis of the sample.

Statistical Analysis

Descriptive statistical analysis was performed using proportions and measures of central tendency and dispersion, according to the nature of the variables.

Linear regressions were conducted to ascertain how each determinant predicts frailty total score and scores per domain. Hierarchical multiple regression analysis were also performed, consisting mainly of five steps: in the first one, sociodemographic characteristics and life events were entered as predictors; second, assessment of lifestyle and satisfaction with living environment; third, self-reported comorbidity; fourth, number of daily-consumed drugs; and fifth, types of medication. In a secondary analysis, the MMSE score was inserted in a sixth step, in order to control for cognitive status.

As in previous studies (Gobbens et al., 2010d, 2012), life event "serious illness in the last year" was excluded from the analysis because it overlaps with comorbidity. Likewise, marital status was not considered for the prediction of total frailty and social frailty because it is closely linked with the TFI item "living alone." Variables that revealed low frequencies (<5%) in the descriptive analysis were excluded in the regression models.

Two-tailed tests were used throughout all analyses and a p-value < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

Descriptive Analysis

The mean age of the participants was 79.2 years (±7.3), and they were mostly women (75.8%), widowed (55.6%), and with low education level (63.9%). The most common monthly household income was 251–500 euros (32.9%). The most shared life event (28.2%) was "serious illness in a loved one," most described their lifestyle as healthy (54.4%), and were satisfied with their home living environment (79.0%). The majority of these elderly reported the presence of two or more chronic illnesses (53.2%), and the mean number of different daily-consumed medications was 5.3 (±3.1). The most frequent medications in this sample have been prescribed for the cardiovascular system (78.6%), nervous system (59.9%) and blood and blood forming organs (40.9%). The mean frailty total score was 6.0 (±3.4), and 2.9 (±2.2), 1.7 (±1.1), and 1.4 (±1.0) for the physical, psychological and social domains respectively. The mean MMSE score was 23.6 (±4.9), and regarding the Barthel Index and the Lawton and Brody Scale, the mean scores were 19.0 (±1.5) and 17.5 (±5.6), respectively. Finally, the mean BMI of the participants was 28.6 (±5.4). **Table 1** provides a more detailed description of the participants' characteristics.

TABLE 1 | Characteristics of the participants ($n = 252$) in regard to Determinants of frailty, frailty, medication.

Characteristics	*n* (%)
Determinants of frailty (TFI part A)	
Age (years), mean ± SD	79.2 ± 7.3
65–74	68 (27.0)
75–84	116 (46.0)
≥85	68 (27.0)
Sex (women)	191 (75.8)
Nationality (Portuguese)	251 (99.6)
Marital status	
Married/living with partner	49 (19.4)
Unmarried	24 (9.5)
Separated/divorced	39 (15.5)
Widow/widower	140 (55.6)
Education (years), mean ± SD	4.4 ± 3.6
0	36 (14.3)
1–4	161 (63.9)
≥5	55 (21.9)
Monthly household income (euros)	
≤250	20 (7.9)
251–500	83 (32.9)
501–750	50 (19.8)
751–1000	44 (17.5)
1001–1500	25 (9.9)
1501–2000	22 (8.7)
≥2001	8 (3.2)
Life events	
Death of a loved one	55 (21.8)
Serious illness	56 (22.2)
Serious illness in a loved one	71 (28.2)
End of important relationship	8 (3.2)
Traffic accident	1 (0.4)
Crime	14 (5.6)
Lifestyle self-assessment	
Healthy	137 (54.4)
Not healthy, not unhealthy	92 (36.5)
Unhealthy	23 (9.1)
Satisfaction with living environment	199 (79.0)
Self-reported comorbidity	134 (53.2)
Frailty (TFI part B)	
TFI total score (0–15), mean ± SD	6.0 ± 3.4
TFI physical domain score (0–8), mean ± SD	2.9 ± 2.2
TFI psychological domain score (0–4), mean ± SD	1.7 ± 1.1
TFI social domain score (0–3), mean ± SD	1.4 ± 1.0
Medication	
Number of daily-consumed medication, mean ± SD	5.3 ± 3.1
Types of daily-consumed medication	
Cardiovascular system	198 (78.6)
Nervous system	151 (59.9)
Metabolism	74 (29.4)
Musculoskeletal system	60 (23.8)
Digestive system	93 (36.9)
Blood and blood forming organs	103 (40.9)
Respiratory system	29 (11.5)

(Continued)

TABLE 1 | Continued

Characteristics	*n* (%)
Genitourinary system	19 (7.5)
Endocrine system	20 (7.9)
Other	23 (9.1)
Cognitive status	
MMSE (0–30), mean ± SD	23.6 ± 4.9
Functional status	
Barthel Index (0–20), mean ± SD	19.0 ± 1.5
Lawton and Brody Scale (0–23), mean ± SD	17.5 ± 5.6
Nutritional status	
BMI (kg/m^2), mean ± SD	28.6 ± 5.4

Regression Analysis

First, due to the low percentage of non-Portuguese individuals, nationality was excluded from the regression analysis. Likewise, life events "divorce or end of important relationship" and "traffic accident" were left out due to the same reason. Also resulting from the descriptive analysis, the last two categories of income "1501–2000" and "≥2001" were regrouped in the single category "≥1501" before inclusion in the regression models. A dummy variable "cohabit" ("1" for married/living with partner and "0" for unmarried, separated/divorced and widow/widower) was created as an alternative to marital status. A dummy variable for sex was also created ("1" for women and "0" for men), and lifestyle was rated "1" for "healthy," "2" for "not healthy, not unhealthy," and "3" for "Unhealthy." Preliminary analysis showed that the effects of education, income and lifestyle were linear, whereas the effects of age were both linear and quadratic. Consequently, age was squared and centered to allow the analysis of both effects on the regression models.

Table 2 presents the effects of the determinants on TFI total score and their significance in the four steps of the hierarchical regression. The first one showed that age had a quadratic effect on frailty, with the youngest and oldest participants having less frailty. Women were, on average, frailer than men, as well as those who experienced the death of a loved one in the last year. On the other hand, as monthly income increases, frailty levels decrease. Education and life events "serious illness in a loved one" and "crime" had no effect on frailty. A total of 17.2% of frailty was predicted in the first step. In the second step, an additional 22.9% was predicted. Unhealthy lifestyle and dissatisfaction with living environment were associated with higher frailty. By including self-reported comorbidity in the third step, 5.9% of the variance of frailty was further predicted, with the presence of comorbidity being associated with a higher degree of frailty. By adding the amount of daily-consumed medication, an additional 2.5% of frailty was predicted, while the effect of age on frailty was no longer significant. As hypothesized, a higher number of medications was associated with higher frailty levels. However, after including the types of drugs in the regression model, the independent effect of the number of daily-consumed drugs on total frailty was no longer significant. In this last step, an additional 4.2% of frailty was predicted, with significant contributions of the variables concerning medications for the cardiovascular system and for the blood and blood forming organs. Frailty was lower in the participants that consumed drugs such as diuretics and ACE inhibitors, and higher for those who consumed drugs such as antiplatelets and anticoagulants.

In regard to physical frailty, a total of 51.3% of TFI physical domain score was predicted (step 1: $\Delta R^2 = 14.2\%$; step 2: $\Delta R^2 = 19.7\%$; step 3: $\Delta R^2 = 5.9\%$; step 4: $\Delta R^2 = 5.3\%$; step 5: $\Delta R^2 = 6.2\%$). In the last model, physical frailty was associated with age (positive linear effect), death of a loved one in the last year, unhealthy lifestyle, dissatisfaction with living environment, self-reported comorbidity, higher amount of medications and, likewise to total frailty, non-consumption of drugs for the cardiovascular system and consumption of drugs for the blood and blood forming organs. The quadratic effect of age was no longer significant after adding lifestyle and satisfaction with living environment, whereas sex and education no longer contributed to physical frailty prediction after adding self-reported comorbidity. Income, serious illness in a loved one, crime, cohabitation and other types of medication had no effect on physical frailty.

Psychological frailty was significantly higher in women, in participants who had experienced the death of a loved one in the last year, had an unhealthy lifestyle, weren't satisfied with living environment and reported comorbidity. The effect of education was only significant in the first step, whereas the contribution of age, income, cohabitation, the remainder life events and the number and type of medications was non-significant throughout all the steps. A total of 25.3% of TFI psychological domain was predicted in the first three models (step 1: $\Delta R^2 = 10.8\%$; step 2: $\Delta R^2 = 11.9\%$; step 3: $\Delta R^2 = 2.6\%$).

Likewise, the variables concerning daily-consumed medication did not contribute to the prediction of social frailty. Remarkably, neither did self-reported comorbidity. A total of 27.7% was predicted in the first two steps (step 1: $\Delta R^2 = 19.3\%$; step 2: $\Delta R^2 = 8.4\%$). Social frailty was associated with age (quadratic effect), being female, higher levels of education, lower income, lifestyle and satisfaction with living environment.

Finally, the effect of the MMSE score on frailty in general and each frailty domain was non-significant, and its inclusion in the regression models (in a sixth step) did not influence the previously observed relationships between variables.

Discussion

A significant proportion of frailty was predicted by life course determinants and by comorbidity. It was also possible to ascertain that each determinant played a different role in the prediction of frailty in general and in each frailty domain. This provides robust evidence to support the integral conceptual model of frailty (Gobbens et al., 2010c). On the other hand, the number of daily-consumed drugs was independently associated with physical frailty, and the consumption of medication for the cardiovascular system (e.g., antihypertensives) and for the blood and blood-forming organs (e.g., antithrombotics) explained part of the variance of total and physical frailty.

TABLE 2 | Results of hierarchical regression analysis on frailty.

Determinants	Model 1			Model 2			Model 3			Model 4			Model 5		
	b	95%CI	*r*	*b*	95%CI	*r*	*b*	95%CI	*r*	*b*	95%CI	*r*	*b*	95%CI	*r*
Age															
Linear effect	0.02	−0.04; 0.08	0.03	0.02	−0.03; 0.07	0.05	0.04	−0.01; 0.09	0.08	0.04	−0.01; 0.09	0.07	0.04	−0.01; 0.09	0.07
Quadratic effect	−0.01**	−0.02; 0.00	0.16	−0.01*	−0.01; 0.00	−0.13	−0.01*	−0.01; 0.00	−0.10	−0.01	−0.01; 0.00	−0.08	0.00	−0.01; 0.00	−0.07
Sex (women vs. men)	1.41**	0.46; 2.35	0.17	1.25**	0.43; 2.06	0.16	0.95*	0.17; 1.74	0.11	1.03**	0.26; 1.80	0.12	0.84*	0.04; 1.64	0.09
Education	−0.11	−0.24; 0.01	−0.10	−0.09	−0.20; 0.02	−0.09	−0.06	−0.16; 0.04	−0.05	−0.03	−0.14; 0.07	−0.03	−0.06	−0.16; 0.05	−0.05
Monthly household income	−0.43**	−0.71; −0.15	−0.18	−0.35**	−0.59; −0.11	−0.15	−0.31**	−0.54; −0.08	−0.13	−0.32**	−0.55; −0.10	−0.13	−0.29*	−0.52; −0.07	−0.12
Life events															
Death of a loved one	1.15*	0.15; 2.14	0.13	1.01*	0.16; 1.86	0.12	1.08**	0.27; 1.90	0.13	1.05**	0.26; 1.85	0.12	0.94*	0.14; 1.74	0.10
Serious illness in a loved one	0.30	−0.61; 1.22	0.04	0.20	−0.58; 0.99	0.03	0.15	−0.60; 0.89	0.02	0.07	−0.66; 0.80	0.01	0.21	−0.51; 0.043	0.03
Crime	0.25	−1.49; 2.00	0.02	0.31	−1.18; 1.80	0.02	0.06	−1.36; 1.48	0.00	−0.02	−1.41; 1.37	−0.00	−0.24	−1.62; 1.13	−0.02
Lifestyle				1.73***	1.18; 2.28	0.31	1.48***	0.95; 2.01	0.26	1.41***	0.90; 1.93	0.25	1.41***	0.89; 1.92	0.24
Satisfaction living environment				−2.35***	−3.22; −1.49	−0.27	−1.96***	−2.80; −1.12	−0.22	−2.01***	−2.83; −1.19	−0.22	−2.01***	−2.84; −1.19	−0.22
Self-reported comorbidity							1.82***	1.11; 2.52	0.24	1.39***	0.66; 2.12	0.17	1.66***	0.91; 2.41	0.20
Amount of drugs										0.20***	0.08; 0.31	0.16	0.17	−0.02; 0.37	0.08
Types of medication															
Cardiovascular system													−1.18*	−2.11; −0.25	−0.11
Nervous system													0.53	−0.21; 1.27	0.06
Metabolism													0.54	−0.26; 1.34	0.06
Musculoskeletal system													0.44	−0.37; 1.25	0.05
Digestive system													−0.13	−0.91; 0.65	−0.01
Blood and blood forming organs													0.82*	0.08; 1.55	0.10
Respiratory system													−0.45	−1.52; 0.61	−0.04
Genitourinary system													−0.89	−2.23; 0.45	−0.06
Endocrine system													−0.07	−1.26; 1.13	0.00
ΔR^2 (%; *p*-value)			17.2***			22.9***			5.9***			2.5***			4.2*

*Regression coefficient (b), semi-partial correlation coefficient (r) and p-value for each determinant, and coefficient of determination change (ΔR^2) and p-value for each model. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

The observed effect of age on frailty was complex. As in other studies (Avila-Funes et al., 2008; Gobbens et al., 2010d; Collard et al., 2012), physical frailty was associated with increased age. This result was expected considering the physical toll of aging (Fried et al., 2009). However, total frailty was highest in participants aged between 75 and 84 years old, mainly because of the higher social frailty observed in this group. In fact, most of the participants who lived alone were included in this age group, possibly due to the fact that most of the younger participants still lived with their spouses, and that many older and widowed individuals lived with younger family members in order to receive the support needed to overcome their physical impairments. Nonetheless, the fact that age was no longer significant in frailty prediction after adding medication to the regression analysis, indicates that other determinants, including comorbidity, better explain the variance of frailty.

Similarly to previous research (Puts et al., 2005; Song et al., 2010; Collard et al., 2012), women were frailer than men. It has been shown that elderly men have a greater likelihood of dying suddenly, while women more often show a steady progressive decline, associated with an increase in morbidity (Puts et al., 2005). This fact can explain the present findings, including why the initial sex-based difference in physical frailty has disappeared after controlling for comorbidity.

As expected (Fried et al., 2001; Woo et al., 2005; Avila-Funes et al., 2008), frailty was also associated with lower income. On the other hand, education had a remarkably positive linear effect on the social frailty domain. This result was surprising considering that in previous research the association of education with frailty was either non-significant (Gobbens et al., 2010d; Garcia-Garcia et al., 2011), or negative (Fried et al., 2001; Woo et al., 2005; Barreto Pde et al., 2012), with lower education levels predicting higher frailty. The present finding may be explained by different views and expectations of social support and relationship quality, from individuals with distinct education levels.

Death of a loved one was the only life event associated with frailty. Considering the well-documented physical and psychological impact of bereavement (Stroebe et al., 2007), it is understandable that this event could lead to frailty. Concomitantly, unhealthier lifestyle and dissatisfaction with living environment predicted frailty in general and in each domain. This provides further evidence of the previously described importance of health-related behavior (Avila-Funes et al., 2008; Fried et al., 2009; Gobbens et al., 2010d) and environmental factors (Hogan et al., 2003; Markle-Reid and Browne, 2003; Bergman et al., 2007) in precipitating frailty.

Self-reported comorbidity, as in previous research (Gobbens et al., 2010d), predicted frailty in general, as well as physical and psychological frailty. Most authors agree that comorbidity can lead to the onset of frailty (Bergman et al., 2007; Fried et al., 2009; Morley et al., 2013). Nonetheless, as described in other studies (Kriegsman et al., 1996), assessing comorbidity trough self-report may be susceptible to bias, mainly because of its dependence on the participants' insight regarding chronic disease. Consequently, as it is directly linked with the amount of comorbidities, the number of daily-consumed drugs might have been a more precise indicator of the participants' health status. Moreover, considering that self-reported comorbidity was rated dichotomously (yes/no), the assessment of the amount of consumed drugs not only is more accurate, but also allows a broader characterization of the heterogeneity of the participants' comorbidity burden.

In fact, as hypothesized, the assessment of medication allowed the prediction of an additional variance of frailty, mainly because of the higher physical frailty of individuals who take greater amounts of medication. It can be discussed that assessing medication, a less subjective measure than self-reported comorbidity, was associated with the less subjective domain of frailty. Nonetheless, one should consider that these findings may also be linked with the adverse outcomes of polymedication and its association with frailty (Gnjidic et al., 2012a,b).

Frailty in general and physical frailty were also predicted by the consumption of medication for the cardiovascular system and for the blood and blood-forming organs. Considering that the latter medication type includes the antiplatelet drugs, which are the mainstay of cardiovascular disease prevention (Lin et al., 2010; Renda and de Caterina, 2012), it is possible to conclude that frailty was independently associated with the usage of drugs that target cardiovascular risk. Indeed, previous research (Fried et al., 2001; Afilalo et al., 2009; Solfrizzi et al., 2013) has shown that frailty – particularly physical frailty – may be associated with common cardiovascular diseases and with their own determinants.

Frailty was lower for those medicated for the cardiovascular system and higher for those who consumed antiplatelet drugs. Although there is limited evidence in this regard, one could argue that the drugs included in the first group were effective in minimizing cardiovascular risk factors and, therefore led to the prevention or to the decrease of frailty (Strandberg and Pitkala, 2007; Afilalo et al., 2009). Moreover, there are studies that suggest that ACE inhibitors improve physical function in elderly individuals, particularly regarding frailty related components, such as mobility and muscle strength (Hutcheon et al., 2002; Onder et al., 2002; Sumukadas et al., 2007). On the other hand, the results regarding the increased frailty of the participants who consumed antiplatelet drugs may be explained by the likely higher cardiovascular risk of these individuals. In fact, according to European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Perk et al., 2012), antiplatelet therapy, particularly low-dose of acetylsalicylic acid, should be prescribed to hypertensive patients with a history of cardiovascular events, with reduced renal function or with high cardiovascular risk. Furthermore, previous research (Burgess et al., 2007) has shown that the consumption of antithrombotics is associated with history of atrial fibrillation and stroke, which in turn can lead to frailty (Woods et al., 2005; Afilalo et al., 2009).

The main strengths of the present study are the statistical procedures used, the reinforcement of the current evidence supporting the multidimensional nature of frailty and of its predictors, and the findings regarding an ameliorated prediction of frailty based on an objective, easy to execute, assessment of medication. It is also the first study that analyzes the determinants

considered in the integral conceptual model of frailty in elderly individuals from a southern European country. Some limitations of this study should be also noted. First, the non-probabilistic sampling method could have limited these findings namely in regard to their generalization. Moreover, in the present study, the proportion of women (75.8%) is considerably larger than the proportion of men. However, this difference roughly reflects the current sociodemographic characteristics of the Portuguese elderly population, in which there is an increasingly larger proportion of women in older age groups (INE, 2012). On the other hand, correlation coefficient values were somewhat low, probably due to the small sample size. Also, the cross-sectional design does not allow the examination of the temporal continuum between determinants, comorbidity, consumed medications and frailty, in order to conclude causality. In turn, the definition of broad medication types/groups could have limited the results. For example, the inclusion of antidiabetics as well as vitamins and mineral supplements in the same group could have limited the ability of this medication type to explain frailty variance. Taking this into consideration, as elderly individuals with diabetes tend to have a greater risk of becoming frail (Fried et al., 2001; Woods et al., 2005), an association would be expected if only antidiabetics were considered. Finally, the self-report nature of TFI can be considered a limitation because of its inherent subjectivity and reliance on memory and insight (Farias et al., 2005; Frank et al., 2011; Antoine et al., 2013). Nonetheless, TFI items correlated as expected with corresponding standardized measures in previous research (Gobbens et al., 2010e; Coelho et al., 2014) and, in the present study, the relationship between self-reported determinants and frailty was not significantly influenced by cognitive status.

Several directions for future research can be suggested. Longitudinal studies should be conducted to better examine how life course determinants and comorbidity predict frailty in the short, medium, and long term. Also, further studies should focus on the association of comorbidity and medications with the psychological and social domains of frailty. Likewise, the association between level of education and each frailty domain should be thoroughly analyzed, especially considering the findings of this study in regard to social frailty.

Conclusion

This research provides important data about which factors may precipitate states of higher vulnerability in this elderly sample. Furthermore, the added value of a brief assessment of medication was significant, so it should be considered as supplementary to TFI. These findings should be taken into account for a more effective identification of frailty, and to implement timely and targeted interventions in order to treat this syndrome and prevent related adverse outcomes.

Author Contributions

TC, CP and LF designed the study. TC was responsible for data collection, carried out the statistical analysis, and drafted the paper. CP and LF supervised the whole research and assisted with interpreting data and writing the article. RG provided advice and aided in the preparation of the final manuscript. All authors reviewed and provided valuable contributions to the whole manuscript.

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Mismatch negativity latency as a biomarker of amnestic mild cognitive impairment in Chinese rural elders

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The aim was to evaluate the mismatch negativity (MMN) component, a correlate of the automatic detection of changes in the acoustic environment, in healthy adults, and adults with amnestic mild cognitive impairment (aMCI). Forty-three aMCI subjects and 43 healthy Chinese older adults were arranged into experimental group and control group, respectively. Their MMN amplitude and latency were measured at the FZ, FCZ, and CZ electrode sites under a passive auditory oddball task. The results showed that the latencies obtained from the FZ, FCZ, and CZ electrode sites were significantly longer in the aMCI adults than in the control adults ($P < 0.01$) while there were no significant differences in MMN amplitude between two groups ($P > 0.05$). The MMN latency was found to be a sensitive and specific biomarker of aMCI.

Keywords: amnestic mild cognitive impairment, Alzheimer's disease, event-related potentials, mismatch negativity, biomarkers

INTRODUCTION

Mild cognitive impairment (MCI) refers to the gray zone between the cognitive changes of normal aging and very early dementia (Grundman et al., 2004a; Stephan et al., 2013). Individuals with MCI show cognitive impairment greater than expected for their age, but otherwise are functioning independently and do not meet the commonly accepted criteria for dementia (Petersen et al., 1999).

The incidence of MCI ranges from 1 to 6% per year while prevalence estimates range from 3 to 22% per year in western developed countries (Hanninen et al., 2002; Larrieu et al., 2002; Ganguli et al., 2004; Roberts et al., 2012). Recently, one large cross-sectional study (Jia et al., 2014) conducted in China, using a multistage cluster sampling design, included a total of 10,276 community residents (6096 urban, 4180 rural) aged 65 years or older, found a prevalence rate of 20.8% for MCI in Chinese elders. The study also stated that rural population had a higher prevalence of overall MCI than urban population (23.4 vs. 16.8%). CRCA (China Research Center on Aging, 2014) has estimated that 1 of every 9 persons is 65 years old or over, totaling 119 million people at the end of 2010 in China. By the year 2050, those numbers are projected to double with the actual number of people over age 65 projected to be almost 300 million, at which point the population of older persons will be accounted for almost 22% of the Chinese population (2014). As the high prevalence of MCI in Chinese rural elders and the rate at which the Chinese population is aging has accelerated, we can forecast that there would be a huge population (about 35.1 million) of elders with MCI by the year 2050 in the rural of China. However, with the progressive urbanization of china, more medical support will be supplied for urban meanwhile medical resources will be even more sparse in rural areas. As a result, the MCI patients in rural areas can hardly get medical help.

Among the different subtypes of MCI, amnestic mild cognitive impairment (aMCI) is the most likely to progress to Alzheimer's disease (AD) (Albert et al., 2011), which is the most prevalent form of dementia in the elderly (Papaliagkas et al., 2009). Subjects with aMCI develop dementia at 10–15% per year (Grundman et al., 2004b; Misra et al., 2009) as compared to the general population of 1–2% (Bischkopf et al., 2002). Delaying or preventing the onset of dementia by a mere 1 year alone could translate into one million fewer number of cases than predicted by the year 2050 (Brookmeyer et al., 1998).

Thus, Biomarkers are needed to facilitate early identification of aMCI and predict progression to dementia. The methods used to search for biomarkers of aMCI include scales (Duchesne et al., 2005; Hoops et al., 2009; Kasten et al., 2010), neuroimaging techniques (Small et al., 2006; Hamalainen et al., 2007), cerebrospinal fluid analysis (Perneczky et al., 2011), and genetic analysis (Zhang et al., 2012), which are invasive or expensive or requires a high level of education, could not be widely used in rural population. Hence, the identification of objective biomarkers that are sensitive to the pathophysiological changes in aMCI and easily accepted in rural population is important for both prevention of dementia and promotion of health.

Mismatch negativity (MMN) relates to the difference wave obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP and usually peaks between 150 and 250 ms after presentation of the deviant stimulus (Nagai et al., 2013). On electroencephalogram (EEG), maximal MMN responses are evident at front central scalp recording sites, with phase reversal at mastoids (Nagai et al., 2013).

Whether MMN technique would be such aMCI biomarkers warrant consideration founded on three essential characteristics designated as ideal (Lindin et al., 2013): it is non-invasive, simple to

measure, and inexpensive. Moreover, MMN is even elicited under passive conditions when subjects ignore the stimuli, which means it does not need the cooperation of participants and it would not be limited by educational level of participants.

Previous studies have shown that MMN is a promising biomarker candidate for cognitive impairment in Parkinson's disease (Cai et al., 2004), brain trauma (Wijnen et al., 2007), Alzheimer disease (Tales et al., 2008), and schizophrenia (Umbricht and Krljes, 2005). In these reported researches, the MMN latencies and (or) amplitude were significantly different between experimental group and control group. Despite the increasing number of research about MMN in other diseases, there are only two published studies to date evaluating the effect of MCI on MMN parameters. Mowszowski et al. (2012) recorded ERPs in an Australia sample of 14 healthy adults and 28 adults with MCI, in a passive oddball task in which the standard and deviant stimuli differed in duration (standard: 50 ms, deviant: 100 ms). They did observe that at mastoid locations, the MMN amplitude was smaller in the MCI group than in the control group, which the authors considered reflect of the inefficiency of processing information in an early pre-attentional stage in the MCI group. Lindin et al. (2013) studied MMN component in Spain healthy adults and adults with aMCI (age range: 50–87 years) using auditory–visual attention–distraction task and found that MMN amplitude at the Cz electrode site was significantly smaller in the aMCI adults than in the control adults, suggesting MMN to be a sensitive and specific biomarker of aMCI.

The recent two studies provided some interesting results, but also presented some limitations. Thus, the former study obtained MMN amplitude at mastoid electrodes, but not at the frontocentral locations, where MMN is typically identified and analyzed (Mowszowski et al., 2012); although the latter study obtained MMN at the frontocentral locations, they only evaluated it at the CZ electrode site, and did not take into account the possible effects of interactions between the electrode sites (FZ, FCZ, CZ) and Group factors (Lindin et al., 2013). Moreover, these two studies were carried out in Australia and Spain, respectively; further researches would be needed in Chinese population.

The aims of the present study were as follows: (1) to determine any differences in MMN parameters between healthy adults and adults with aMCI in Chinese rural population; (2) to evaluate whether such differences between healthy adults and adults with aMCI are affected by electrode sites, by considering three electrode sites (FZ, FCZ, CZ); (3) to evaluate whether MMN changes associated with aMCI are sensitive and specific biomarkers of this syndrome.

MATERIALS AND METHODS

PARTICIPANTS

Forty-three aMCI subjects and 43 healthy Chinese older adults selected from rural villages of Weifang, Shandong, China were arranged into experimental group and control group, respectively.

Experimental group: there were 22 male and 21 female subjects in this group, the average age was 65.81 ± 6.90 years and the average years of education were 3.88 ± 2.80. The participants were selected according to the U.S. mental disorders' fourth edition of the Diagnostic and Statistical Manual (DSM-IV) (Association and DSM-IV, 1994) in mild neurocognitive damage standards and the Diagnosis standard of Shanghai Mental Health Center (Shi Fu and Wei, 1999): (1) memory complaints corroborated by an informant; (2) Mini-Mental State Examination (MMSE) Score $\leq$26 points, the level of Global Deterioration Scale (GDS) assessment is between 2 and 3; (3) activity of daily living scale (ADL) Score $\leq$18 points; (4) Hachinski ischemia index (HIS) $\leq$4 points; (5) course of cognitive impairment $>$3 months; (7) Does not meet DSM-IV (1) criteria for dementia syndrome.

Control group: there were 19 male and 24 female subjects in this group, the average age was 66.21 ± 6.81 years and the average years of education were 4.90 ± 2.76. The participants were selected according to the following criteria: (1) no memory complaint; (2) MMSE total score $\geq$24; (3) intact instrumental activities of daily living.

Subjects with any of the following condition were excluded from the study: (1) left-handed; (2) visual or hearing difficulty; (3) depression; (4) history of head trauma; (5) heart, lung, liver, or kidney failure; (6) active neurological or psychiatric conditions; (7) any severe illness that may affect cognitive function; (8) drug or alcohol abuse.

Ethical approval for this study was obtained from the Research Ethics Committee, Weifang Medical University, and written informed consents were obtained from all of the subjects.

There were no significant differences in gender, age, or educational level between the experimental and control groups as shown in **Table 1**.

STIMULI AND TASK

A passive auditory oddball task was used in this study. Participants were presented with 500 auditory stimuli (divided in two blocks separated by a 2-min rest interval). Auditory stimuli were sounds, presented binaurally via headphones. Two kinds of sounds were presented: 85% were standard stimuli (tone bursts, 1000 Hz, 85 dB) and 15% were deviant stimuli (tone bursts, 2000 Hz, 90 dB).

ELECTROENCEPHALOGRAPHIC RECORDING

The participants were seated on a comfortable chair in a Faraday chamber, with attenuated levels of light and noise, and were instructed to move as little as possible during the recording. The EEG was recorded from 64 ring electrodes placed in an elastic cap, according to the International 10–20 system. All electrodes were referenced to an electrode attached to the tip of the nose, and an electrode positioned at Fpz served as ground. The vertical electrooculogram (EOG) was recorded from two electrodes placed supra and infra-orbitally on the left eye, and the horizontal EOG was recorded from two electrodes placed at the outer canthi of both

Table 1 | Characteristics of the study sample (aMCI vs. HC).

Variable	aMCI	HC	*P*
Age	65.81 ± 6.90	66.21 ± 6.81	0.787
Female	21 (49%)	24 (56%)	0.517
Education (years)	3.88 ± 2.80	4.90 ± 2.76	0.093

aMCI, amnestic mild cognitive impairment; HC, healthy controls.

eyes. The EEG was continuously digitized at a rate of 1000 Hz (band pass 0.05–100 Hz), and electrode impedances were kept below 5 kΩ. Finally, to identify and measure MMN, we obtained the deviant minus standard (D − S) difference waveforms. The MMN component was identified as a negative wave in the 100–250 ms interval, and it was evaluated at the FZ, FCZ, and CZ electrode sites, respectively. The MMN amplitude (in microvolts, from the maximum peak to the baseline) and latency (in milliseconds, from the auditory stimulus onset to the maximum peak) were measured.

STATISTICAL ANALYSIS

Repeated measure analysis of variance (ANOVA) was conducted to investigate the effect of the Group (Experimental group, Control group) and Electrode Sites (FZ, FCZ, CZ) factors on the MMN amplitude and latency. The comparison on various characteristics was conducted using Student's test (for continuous variables) or chi-square test (for dichotomous variables). All statistical analysis was performed using SPSS 18.0. Differences were considered significant at $p < 0.05$.

RESULTS

MMN LATENCY

The grand average MMN wave forms for aMCI and healthy controls are shown in **Figure 1**, healthy adults in the current study have a negative-going MMN in the 100–250 ms time window at the FZ and FCZ electrode while aMCI patients showed no clear MMN. For MMN latency, repeated ANOVA (Group × Electrode Sites) showed significant effects of the Electrode Sites factor ($F = 61.984$, $P < 0.001$), the Group factor ($F = 197.573$, $P < 0.001$), and the Group × Electrode Sites interaction ($F = 11.728$, $P < 0.001$) (**Table 2**). The latencies obtained from the FZ, FCZ, and CZ electrode sites were significantly longer in the MCI group than in the control group ($P < 0.05$) (**Table 3**). For the aMCI group, FZ latency > FCZ latency > CZ latency ($P < 0.01$); for the control group, FZ latency > CZ latency ($P < 0.01$) and FCZ latency > CZ latency ($P < 0.01$), but there was no significant difference between FZ latency and FCZ latency ($P > 0.05$) (**Table 3**).

MMN AMPLITUDE

Repeated ANOVA (Group × Electrode Sites) showed significant effects of the Electrode Sites factor ($F = 25.770$, $P < 0.001$), but there was no significant Group factor ($F = 0.688$, $P > 0.05$) or Group × Electrode Sites interaction ($F = 2.586$, $P > 0.05$) (**Table 2**).

DISCUSSION

Mismatch negativity component was identified in both groups of participants (control and aMCI). Control and aMCI adults showed differences for MMN component, healthy adults in the current study have a negative-going MMN with an evident peak in the 100–250 ms time window at the FZ electrode while aMCI patients showed no clear MMN. However, when compared to the clear MMN peak at −4 μV at Cz in Lindin et al. (2013), the MMN here in the healthy group seems to be not that prominent (−1.5 μV). The reason might be the sample differences of this study and Mónica Lindínl's. The average age of healthy adults in the current study was 66.21 ± 6.81, while the clear MMN peak at −4 μV in Lindin et al. were from the middle-aged subgroup (50–64 years), the MMN from the older age subgroup (65 years and over) was not that prominent either in Mónica Lindín et al.

The MMN latencies obtained from all three electrode sites (FZ, FCZ, and CZ) were significantly longer in the aMCI group than

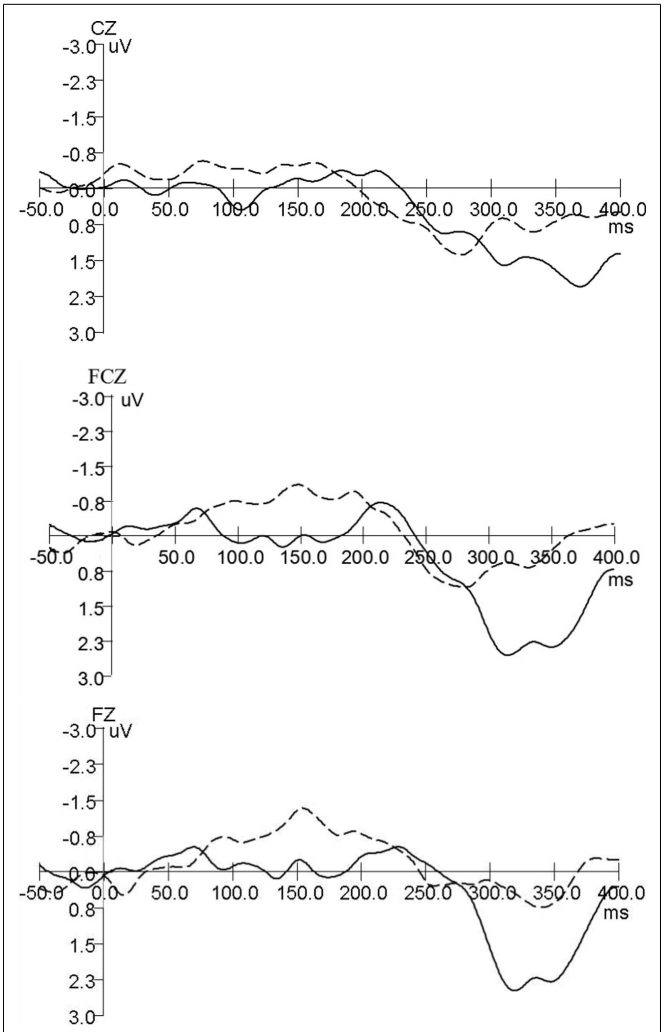

FIGURE 1 | Grand average MMN wave forms for aMCI and healthy controls. Mismatch negativity (MMN) component was identified in both groups of participants (control and aMCI). Control and aMCI adults showed differences for MMN component (— aMCI, . . . healthy controls).

Table 2 | The effects of electrode location and group on ERP amplitude and latency.

Variable	Electrode site	Group	Location × group
MMN amplitude	25.770***	0.688	2.586
MMN latency	61.984***	197.573***	11.728***

This is the main effect (electrode site, group) and interaction effect (electrode site × group) using a two-factor analysis of variance.

Electrode site: FZ, FCZ, CZ; Group: MCI vs. HC.

****Indicates p < 0.001.*

Table 3 | Comparison of MMN latency between aMCI and healthy controls.

Electrode	Latency		
	aMCI	Controls	*P*
FZ	237.47 ± 9.145	197.44 ± 14.730	<0.001
FCZ	227.16 ± 9.947	196.56 ± 13.191	<0.001
CZ	214.21 ± 17.246	188.26 ± 13.510	<0.001

This is the post hoc test results of the mean values of latencies between aMCI and control groups.

in the CG, and the difference is more obvious at the FZ electrode site. This result is intriguing because different results about MMN latencies were reported in the only two previous studies comparing MCI group with a control group. Lindin et al. (2013) reported that the MMN latency was significantly shorter in the aMCI group than in the CG. Mowszowski et al. (2012) also observed slightly shorter (but non-significant) MMN latencies (measured at Fz and Cz electrodes) in the MCI than in the control group. Despite the controversy with the two previous studies, the result of the present study on MMN latency is consistent with previous studies comparing other diseases that may cause cognitive impairment with a control group. Cai et al. (2004) evaluated MCI in Parkinson's disease with MMN and found that the peak latency of MMN in the PD group was significantly longer than in the control group. Kathmann et al. (1995) reported delayed MMN peak latencies in chronic alcoholics, in comparison with their healthy peers. Lou et al. (2006) evaluated MMN of patients with first-episode schizophrenia and reported delayed MMN latency in schizophrenics compared to healthy controls, similar results were found in another research in chronic soldiers' schizophrenics (Gao et al., 2007). Moreover, prolonged latencies were reported in experimental group in the clinical researches of MMN in patients with AD (Chen et al., 2003).

Inconsistent with the two previous studies comparing MCI group with a control group, no significant group factor was found in MMN amplitude in the present study. Mowszowski et al. (2012) observed a larger MMN amplitude in healthy adults than in a multi-domain MCI group (for an age range of 50–90 years in both groups). Mónica Lindín et al. found the MMN amplitude was significantly larger in the CG than the aMCI group, only for the middle-aged subgroup (50–64 years), but not for adults 65 years old or more. The authors tentatively speculate that this is probably due to a significant age-related decrease in MMN amplitude in the CG, as also found by Gaeta et al. (1998). The lack of differences between the CG and the aMCI group may be due to an age-related decline in the mechanism for echoic memory trace maintenance and/or the pre-attentional mechanisms involved in the automatic detection of differences in the acoustic environment, which may mask the effects of aMCI on that parameter (Lindin et al., 2013). This might also be the reason of the present study of no significant group factor in MMN amplitude. Further studies are needed to identify this.

As found in the present study, MMN latencies were significantly longer in aMCI adults, the MMN latency may be considered a biomarker of aMCI. Moreover, the characteristics of the MMN component make it an ideal biomarker; it is an automatic ERP component, which is not dependent on the attention given by the subject to the task and, moreover, it is obtained in a non-invasive manner and is simple and inexpensive to measure. However, in consideration of the discordance between our findings and the two previous studies, which reported earlier (latency) and/or smaller (amplitude) MMNs in the aMCI population (Mowszowski et al., 2012; Lindin et al., 2013), both contrary to the findings of our study, a more in-depth approach to potential ways to address this discordance in future work would be needed to clarify whether MMN latency can be a fairly sensitive and specific psychophysiological biomarker for the identification of adults with aMCI.

This study is not without limitations that mainly include unknown group differences in risk factors of cognitive decline and AD, such as apolipoprotein E e4 genotype, and inflammation, although there were no significant differences between groups in terms of gender, age, or educational level. Besides, in consideration of the relatively small sample size of this study, reference values of MMN latency and amplitude for both aMCI and healthy elders could not be offered. Future studies, with a large sample of participants, should determine reference values of MMN latency and amplitude for aMCI elders.

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REVIEW
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Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis

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Subclinical hypothyroidism (SCH), defined as elevated thyroid stimulating hormone (TSH) and normal thyroid hormone levels, and cognitive impairment are both common in older people. While the relation between overt hypothyroidism and cognitive impairment is well established, data on the association between SCH and cognitive impairment are conflicting. This systematic review and meta-analysis was performed to assess available evidence on the association of SCH with cognition in community dwelling, relatively healthy older adults. PubMed, EMBASE, Web of Science, COCHRANE, CINAHL, PsycINFO, and Academic Search Premier (January 1966 to April 1, 2015) were searched without language restrictions, as were references of key articles, for studies on the association between SCH and cognition in older adults (>60 years). These studies were reviewed by two independent reviewers according to predefined criteria for eligibility and methodological quality, and data were extracted using standardized forms. Of the 844 reports initially identified, 270 remained after exclusion of duplicates. Of the 270, 15 studies comprising 19,944 subjects, of whom 1,199 had subclinical hypothyroidism were included. Data from the 15 studies was pooled, and meta-analyzed cross-sectionally for global cognition [assessed by Mini-Mental State Examination (MMSE)], executive function, and memory, using random effects models. Pooled effect size (ES) for MMSE was −0.01 (95% CI −0.09, 0.08), with heterogeneity (I^2) of 55.1%. Pooled ES was <0.001 (95% CI −0.10, 0.09) for executive function (I^2 = 13.5%), and 0.01 (95% CI −0.12, 0.14) for memory (I^2 = 46.9%). In addition, prospective analysis including four studies showed pooled ES of 0.033 (95% CI −0.001 − 0.067) for MMSE (I^2 < 0.001%), indicating that subclinical hypothyroidism was not significantly associated with accelerated cognitive decline. This systematic review and meta-analysis provides no evidence that supports an association between SCH and cognitive impairment in relatively healthy older adults.

Keywords: cognition, subclinical hypothyroidism, elderly, meta-analysis, systematic review

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Introduction

Overt adult onset hypothyroidism, which is marked by elevated thyroid stimulating hormone (TSH) levels and reduced levels of circulating thyroid hormones, has been associated with increased risk of deficits in specific cognitive domains including attention, concentration, memory, perceptual function, language, executive function, and psychomotor speed (Constant et al., 2005; Davis and Tremont, 2007; Samuels, 2008; Correia et al., 2009). However, controversies persist as to whether subclinical hypothyroidism (SCH), defined as mild elevation of TSH in the presence of normal free thyroxine (fT4), is associated with declines in these specific cognitive domains. This is especially relevant in the older adults, as the prevalence of subclinical hypothyroidism increases with age and is estimated to be up to 22% in women aged more than 60 years and somewhat lower in men (Sawin et al., 1985; Canaris et al., 2000).

Many studies have investigated whether subclinical hypothyroidism is associated with increased risk of cognitive impairment (Manciet et al., 1995; Cook et al., 2002; Gussekloo et al., 2004; Roberts et al., 2006; Cardenas-Ibarra et al., 2008; Hogervorst et al., 2008; Ceresini et al., 2009; John et al., 2009; Park et al., 2010; de Jongh et al., 2011; Resta et al., 2012; Yamamoto et al., 2012; Wijsman et al., 2013; Formiga et al., 2014; Parsaik et al., 2014). However, the data are conflicting, and epidemiological studies that investigated this relationship have reported inconsistent findings. Furthermore, due to use of different TSH cut-off values, methodological differences, application of varying cognitive tests for different cognitive domains, and diverse reporting of results by these studies, the interpretability and comparability of their findings are hindered.

Here, we performed a systematic review of available evidence from both cross-sectional and prospective studies on the association between subclinical hypothyroidism and cognition in the older adults. Furthermore, we performed a meta-analysis to quantify the magnitude of the associations between subclinical hypothyroidism and both global cognition as well as two specific cognitive domains, namely executive function and memory.

Methods

Data Sources and Search Strategy

A systematic literature search was conducted of articles published from January 1966 to April 1, 2015 on the association between subclinical hypothyroidism and cognition in the elderly. PubMed, EMBASE, Web of Science, COCHRANE, CINAHL, PsycINFO, and Academic Search Premier were searched (Datasheet 1). The design of the electronic search strategy was done in consultation with an expert information specialist. A thorough search was conducted on the bibliographies of key articles in the field and these were included in this review. To avoid missing any relevant study in the search, broadly defined terms were used (Datasheet 1). Reference lists of key articles were also searched for relevant articles that could have been missed.

Study Selection

Two independent reviewers (AAA and SWJ) screened the extracted citations for eligibility. To maximize the quality and comparability of the studies, general inclusion and exclusion criteria were defined *a priori* (**Table 1**). The titles, abstracts and later the full-texts of the search results were screened—the studies included were those that assessed the cognitive status of relatively healthy (community dwelling, and considered healthy by the authors of the original articles) elderly (aged 60 years and above) participants with subclinical hypothyroidism.

Subclinical hypothyroidism is defined as elevated TSH and normal fT4 (Helfand, 2004). However, controversies exist as to the upper limit of the TSH reference range. Several reviews suggest a TSH upper limit of 4.5–5.0 mIU/L (Helfand, 2004; Surks et al., 2004), but some authors suggest that the upper limit of the TSH range should be reduced to 2.5–3.0 mIU/L, based on a higher risk of progression to overt hypothyroidism and a higher prevalence of anti-thyroid antibodies than in euthyroid participants (Vanderpump et al., 1995). In the absence of a consensus, the use of a specific TSH upper limit was not pre-specified in this systematic review to define subclinical hypothyroidism. Furthermore, fT4-values were considered normal if indicated as normal by the authors, even if data on fT4 were not presented.

Studies done on participants with depression [according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria], dementia, psychiatric symptoms, neurological disorders e.g. Parkinson's disease, and other chronic systemic illnesses were excluded. Furthermore, participants using thyroid medications were excluded. Three relatively large studies that measured health status of participants with an elevated TSH were initially included. However, they were later excluded because assessment of mood, and general and mental health status was done qualitatively, without specifying whether global cognition or specific cognitive domains were measured (Razvi et al., 2005; Gulseren et al., 2006; Vigario et al., 2009).

Data Extraction and Quality Assessment

From each study that met the eligibility criteria, information was extracted about study design (prospective or cross-sectional), participant characteristics, criteria used to define subclinical hypothyroidism, cognitive tests applied and domains tested, and study results (effect estimates, variables included for adjustments, or matching procedures) using a standardized data-collection form.

The two reviewers (AAA and SWJ) independently assessed the methodological quality of included studies using a pre-defined list of criteria (Egger et al., 1997; Stroup et al., 2000) (Datasheet 2). In total, 11 key indicators were used to systematically assess study quality. These were (1) clarity of hypothesis, (2) population studied (convenience sample vs. population-based, defined as a random sample of the general population), (3) clear definition of subclinical hypothyroidism (indication of TSH cut-off and fT4-values that were used in the study), (4) detailed description of study materials and methods, (5) validity of measurements and cognitive tests, (6) number of cognitive domains tested (global cognition, executive function, and/or memory), (7) clear description of statistical methods, (8) adjustments/correction for potential confounders, (9) clear presentation of results, (10) generalizability to other populations, and (11) method of outcome adjudication [use of formal adjudication procedures,

TABLE 1 | Selection criteria for eligibility for inclusion or exclusion.

Inclusion criteria	Exclusion criteria
Human studies	Animal studies
Median/mean age 60 or above	Younger than 60
Subclinical hypothyroidism (SCH) defined as: - Elevated TSH and normal fT4; - All self-defined subclinical hypothyroidism • Elevated serum TSH in association with normal total or free T4- and T3-values • High-normal TSH and abnormal response to TRH • Elevated serum TSH with normal thyroid hormone levels, without symptoms that could be explained by overt hypothyroidism	SCH not defined
Relatively healthy elderly participants Healthy as determined by the authors of the original articles	Full blown depression, psychiatric symptoms, neurological disorders as Parkinson's disease or predefined dementia, substance abuse
Free living/community dwelling	Hospitalized patients
Original research articles including prospective studies, randomized-controlled trials, etc. that provide baseline data	Systematic reviews, meta-analyses, reviews, conference abstracts, web pages
Cognitive measure and domain specified	Cognitive domain not well defined, e.g. "mood," "quality of life," "mental health" etc.
All languages	
	Duplicates

defined as having clear criteria for the outcome (cognitive impairment)]. A score of "0" (lacking), "1"(incomplete), or "2" (complete) was assigned to each of the key indicators per study, with a maximum total score of 22.

Data Synthesis and Statistical Analysis

Authors were contacted when necessary to request more detailed data on the association between subclinical hypothyroidism and cognition in older adults (Gussekloo et al., 2004; de Jongh et al., 2011; Formiga et al., 2014). The most adjusted estimates and SD/SE were used for analysis, where available. In instances where participants were divided into groups based on TSH-values (tertiles/quartiles), the mean TSH-value for the whole group was used.

Data was qualitatively synthesized and assessed for the number of participants that were included, the definition of subclinical hypothyroidism applied, the cognitive tests that were used and the cognitive domains that were measured. Meta-analysis was done by comparing estimates from participants with subclinical hypothyroidism with those from euthyroid participants, using data from both cross-sectional studies and baseline data from prospective studies for the cross-sectional analysis. Thus, only studies that provided these estimates were included in the meta-analysis. Using Hedges method (Hedges and Vevea, 1998), pooled estimates with standard error were calculated first from cross-sectional analysis of available studies, and then for the prospective data, using the same approach.

To make effect estimates comparable between studies, effect sizes (ES) were calculated from calculated means with standard deviation of participants with subclinical hypothyroidism compared to euthyroid participants. For studies that used >1 cognitive test (Cook et al., 2002; Gussekloo et al., 2004; John et al., 2009; Park et al., 2010; Wijsman et al., 2013; Parsaik et al., 2014), a pooled ES was calculated for each study. After calculating an ES for each study, a meta-analysis was performed using a random effects model. The random effects model was applied, because it takes into account the heterogeneity between the studies. All statistical analyses were performed using STATA version 10. Cochrane Q-test and I^2 index with a conservative p-value of 0.10 were used to evaluate the heterogeneity across individual studies. I^2-values of <25% were considered reflective of low, between 25 and 50% of moderate and >50% of high heterogeneity between studies.

Results

Study Selection

Of the 844 reports initially identified, 270 remained after exclusion of duplicates. Of the 270 reports, 210 were excluded that were unrelated to the association between subclinical hypothyroidism and cognition in the elderly (**Figure 1**), leaving 60 articles for full text analysis. Two more articles were selected from reference lists of relevant articles. Of the 62 articles that were selected for detailed (full text) evaluation, full texts were not

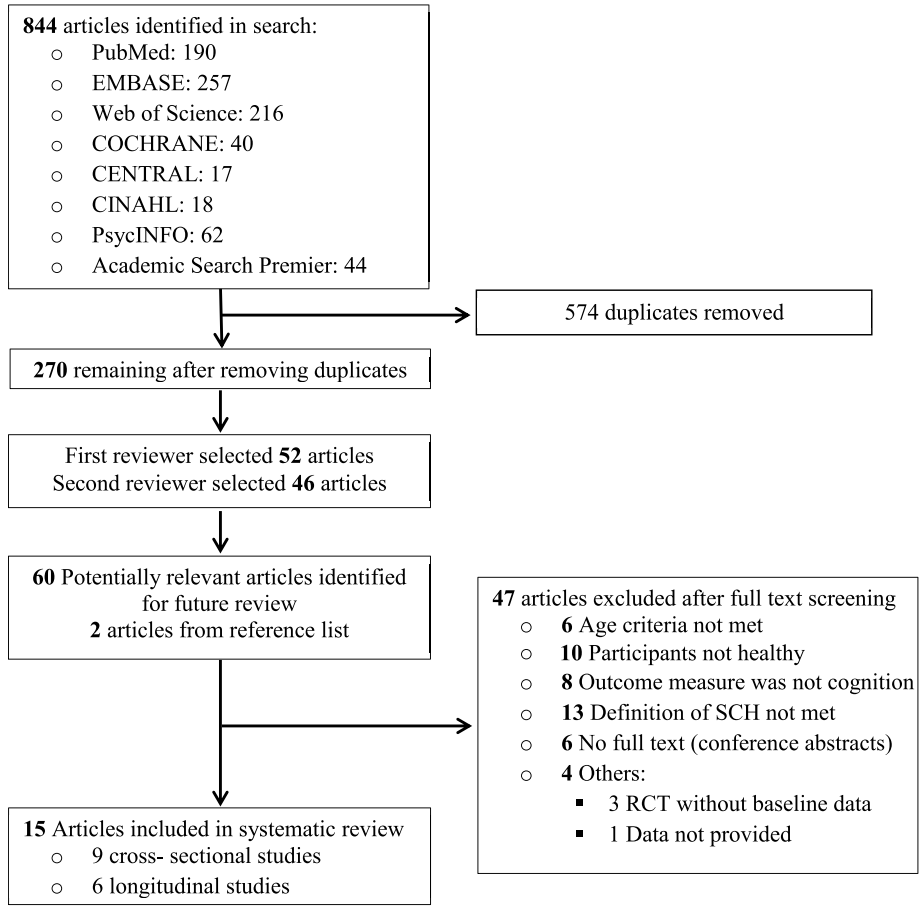

FIGURE 1 | Flowchart showing the literature search for the systematic review.

available for six studies. Additionally, 10 studies were excluded because the participants were not considered healthy, another 13 because the definition of subclinical hypothyroidism (high TSH and normal fT4) was not met and four because data was not available for systematic review [three were randomized controlled trials (RCTs) without baseline data, and one study reported qualitative results]. Furthermore, eight studies that did not measure cognition as endpoint were excluded—these either measured mental health by means of questionnaires, or studied depression. Six other studies were excluded because the mean/median age of the participants was less than 60 years (**Figure 1**).

Two studies each were reported in Spanish and Dutch, respectively, one in Italian and another in Czech. The researchers (AAA and SWJ) themselves translated the two Dutch articles into English. Another article was translated from Czech to English by the author himself (Jensovsky et al., 2000). The other foreign language articles were translated to English by the researchers' colleagues that spoke the language. These articles were all later excluded after full-text analysis. When similar data were published more than once (Gussekloo et al., 2004, 2006; Wiersinga, 2006), the article with the most definitive and extractable data was included (Gussekloo et al., 2004). One study was later dropped because it studied the effect of subclinical hypothyroidism on demented and non-demented elderly using only clinical dementia rating, thus was incomparable with the other selected studies in terms of results (Ganguli et al., 1996). Fifteen observational studies met the eligibility criteria.

Study Characteristics

Table 2 shows the characteristics of the nine cross-sectional and six prospective studies that were included in the review. In total, the 15 studies comprised 19,944 participants, of whom 1,199 had subclinical hypothyroidism. The upper reference limit of TSH (TSH cut-off) to define subclinical hypothyroidism ranged from 3.6 to 10 mIU/L. A total of 13 out of the 15 studies also reported fT4 measurement. The studies used varying cognitive tests to measure a wide range of cognitive domains. The cognitive domains that were covered included global cognition, executive function, memory, general intelligence, attention, and concentration, visio-spatial organization, language, and cognitive or psychomotor speed. These cognitive domains were merged into three main domains, namely global cognition, executive function, and memory, as shown in **Table 3**. The cognitive tests

TABLE 2 | Characteristics of studies included in the systematic review on the association between subclinical hypothyroidism (SCH) and cognitive impairment in older adults.

	First author	Type of study	Study (Follow-up in years)	*N* Total	*N* with SCH	Mean age (Years)	Cut off TSH (ref. range) mIU/l	fT4 pmol/l	Cognition tests	Study quality
1	Roberts et al., 2006	Cross-sectional	N/A*	5865	168	73.6	>5.5	9.0–20.0	MMSE, MEAMS	21
2	Wijsman et al., 2013	Prospective	Prosper study (3 years)	5.154	161	75	>4.5 (0.45–4.5)	12–22	MMSE, Stroop, LDCT, WLT. (Immediate and delayed)	22
3	Parsaik et al., 2014	Cross-sectional	N/A*	1904	141	81	>10	12.87–12.04	WAIS-R: TMT, DSST; BNT, CFT, PCBD, WMS (logical memory I and visual reproduction II)	21
4	Park et al., 2010	Cross-sectional	N/A*	918	164	76	>4.1 (0.4–4.1)	9.0–23.2	MMSE, DS, FAB, CERAD-K-N including CFT, BNT-modified, CPT, WLMT, WLRT, WRLRcT, CRT	19
5	de Jongh et al., 2011	Prospective	Longitudinal aging study, Amsterdam, (10.7 years)	1219	64	75.5	>4.5 (0.3–4.5)	11–22	MMSE, RPM, and the coding task	20
6	Hogervorst et al., 2008	Prospective	MRC cognitive function and aging study (2 years)	1047	33	73.6	>4.8	13–23	MMSE, WMS-revised	20
7	Gussekloo et al., 2004	Prospective	Leiden 85 + study (3.7 years)	558	30	85	>4.8	13–23	MMSE, Stroop, LDCT, WLT (immediate and delayed).	21#
8	John et al., 2009	Cross-sectional	N/A*	489	286	>60	>10.0 (0.3–10.0)	Not indicated	SILS, TMT-b, SDMT, JLO, BD and LNS from WAIS, AN, BNT-modified, CVLT, EBMT, Faces I and II from WMS	17
9	Resta et al., 2012	Cross-sectional	N/A*	391	42	74.3	>3.6 (8.0–17.0 pg/mL)	8.1–15.43	MMSE, PMT, and MT	16
10	Ceresini et al., 2009	Cross-sectional	N/A*	1117	25	77	>4.7	9.9–28.2	MMSE	18
11	Formiga et al., 2014	Prospective	OCTABAIX study (3 years)	328	20	85	>5	10–26	MMSE (MEC, Spanish version)	19#
12	Manciet et al., 1995	Cross-sectional	N/A*	425	26	74.4	>4.5 (0.5–4.5)	16–29	MMSE, WAIS, BVRT, ZBT, IT	16
13	Yamamoto et al., 2012	Prospective	Japanese study (1 year)	229	15	80.9	Not indicated	Not indicated	MMSE, revised hasegawa dementia scale	16

(Continued)

TABLE 2 | Continued

	First author	Type of study	Study (Follow-up in years)	*N* Total	*N* with SCH	Mean age (Years)	Cut off TSH (ref. range) mIU/l	fT4 pmol/l	Cognition tests	Study quality
14	Cook et al., 2002	Cross-sectional	N/A*	97	15	74	4.0 (0.4–4)	Not indicated	MMSE, AVLT, DSCT from WAIS, *N* Back test, backward DS	16
15	Cardenas-Ibarra et al., 2008	Cross-sectional	N/A*	253	9	80	>4.5	Not indicated	MMSE	12

AN, Animal naming; AVLT, Auditory verbal learning test; BD, block design; BNT, Boston naming test; CFT, category fluency test; CPT, constructional praxis test; CRT, constructional recall test; CVLT, California Verbal Learning Test; CVMT, continuous visual memory test; DS, digit spans forward and backward of WAIS-R; DSCT, Digit symbol coding test (from WAIS); DSST, Digit symbol substation test; EBMT, East Boston Memory Test; FAB, Frontal assessment battery; IT, Isaacs set test of verbal fluency; JLO, Judgment of line orientation; LDCT, letter digit coding test; LNS, Letter-number sequencing; LW, list of words; MEAMS, Middlesex elderly assessment of mental state (12 scores); MEC, Mini mental state examination (35 scores); MMSE, Mini-Mental State Examination(30 scores); MMMSE, Modified Mini-Mental State Examination; MT, Matrix test; PMT, Prose memory test; PCBD, Picture completion and block design; RPM, raven progressive matrices test; RW, Rey's words immediate and delayed recall; SDMT, symbol digit modalities test; SILS, Shipley Institute of Living scale; Stroop, Stroop color word test; TMTA&B, trail making test A and B; WAIS, Wechsler adult intelligence scale; WAIS-R, Wechsler adult intelligence scale-revised; WFT, word fluency test; WLMT, word list memory test; WLRT, Word list recall test; WRLRcT, Word list recognition test; WLT, word learning task; WMS, Wechsler memory scale; ZBT, Zazzos barring test.

**N/A: Not applicable.*

#Score based on published and unpublished data provided by the author.

TABLE 3 | Cognitive tests and domains used for meta-analysis.

Cognitive domain	Measures and cognitive tests
Global cognition	MEAMS, MMSE, MMMSE, 3MSE
Memory (including tests for language)	AN, AVLT, CRT, CVMT, DS, EBMT, FMT, IPALT, LDCT, LW, *N*-back test, PMT, PWLT, RCFT, SRT, WLT, RBP, RW, WLMT, WLRT, WMS, WRLRcT, Language: AN, BNT, CFT, CVLT, COWAT, IT, OR, RW, WFT, WD, ZBT
Executive function	BD, FAB, DSST, GNG, LMN, MT, PM, RPM, SILS, TMT, WAIS, WFT, Attention and concentration: CST, DS, LNS, PASAT, SDMT, Stroop, TMTA&B Visuo-spatial organization: CC, CoS, CPT, FR, JLO, HT, PCBD, ScT, SDMT, TMT(Part A), WAIS-R Cognitive or psychomotor speed: DSCT, WAIS-R, TMT(Part A), WFT

AN, animal naming; AVLT, Auditory verbal learning test; BD, block design; BNT, Boston naming test; CFT, category verbal fluency test; COWAT, Controlled oral word; CPT, constructional praxis test; CRT, constructional recall test.; CST, concept shifting test; CVLT, California Verbal Learning Test; CVMT, continuous visual memory test; DS, digit spans forward and backward of WAIS-R; DSCT, Digit symbol coding test (from WAIS); DSST, Digit symbol substitution test; FMT, Milner facial memory test; EBMT, East Boston Memory Test; FAB, Frontal assessment battery; FR, figure rotation from the Schaie-Thurstone adult mental abilities test; GNG, Go-No-Go; HT, Hooper test; IPALT, Inglis paired associates learning test; IT, Isaacs set test of verbal fluency; JLO, Judgment of line orientation; LDCT, letter digit coding test; LMN, Luria m's and n's; LNS, Letter-number sequencing; LW, list of words; 3MSE, Modified MMSE (100 scores); MEAMS, Middlesex elderly assessment of mental state (12 scores); MMSE, Mini mental state examination (30 scores); MMMSE, Modified Mini-Mental State Examination; MT, Matrix test; OR, oral reading; PASAT, paced auditory serial addition task; PM, Porteus maze; PMT, Prose memory test; PCBD, Picture completion and block design; PWLT, picture word learning test; RBP, Rivermead behavioral profile; RCFT, Rey-Osterrieth complex figure test; RPM, raven progressive matrices test; RW, Rey's words immediate and delayed recall; ScT, scribble test; SDMT, symbol digit modalities test; SILS, Shipley Institute of Living scale; SRT, selective reminding test (Buschke); TMTA&B, trail making test A and B; WAIS, Wechsler adult intelligence scale; WAIS-R, Wechsler adult intelligence scale-revised; WD, word discrimination; WFT, word fluency test; WLMT, word list memory test; WLRT, Word list recall test; WRLRcT, Word list recognition test; WLT, word learning task; WMS, Wechsler memory scale; ZBT, Zazzos barring test.

that were used for each of these cognitive domains are also presented in **Table 3**.

Systematic Review

In total, 1,199 participants with subclinical hypothyroidism were included in the systematic review. From the 15 studies in our systematic review, 12 studies indicated a lack of significant association between subclinical hypothyroidism and cognitive impairment in the elderly. These studies comprised 1,109 participants with subclinical hypothyroidism and therefore contributed 92.5% of the population sampled to the outcome of the systematic review. Of the remaining three studies, two found an association, and one was inconclusive (Hogervorst et al., 2008). The inconclusive study demonstrated an association between log transformed TSH levels with decreasing MMSE performance in hypothyroid participants, but it was not specified whether the observed association was with overt

hypothyroidism or with subclinical hypothyroidism. This study was included in the systematic review but excluded from meta-analysis.

A total of two studies found an association between subclinical hypothyroidism and cognition in the elderly. The first study found (in 15 participants with subclinical hypothyroidism) that high TSH levels were associated with worse verbal memory and MMSE scores but not with speed of performance (Cook et al., 2002). The second study found (in 42 participants with subclinical hypothyroidism) that performances in MMSE and Prose memory test were lower in participants with subclinical hypothyroidism compared to euthyroid participants (Resta et al., 2012). Performance in matrix test was also slightly lower in subclinical hypothyroidism, but this was not significant. Summarily, from the studies that observed a significant association between subclinical hypothyroidism and cognitive impairment, the cognitive domains affected were global cognition as assessed via MMSE; executive function as assessed via matrix test; and memory as assessed via auditory verbal learning test, prose memory test, and verbal fluency. The two studies combined comprised 57 participants with subclinical hypothyroidism and contributed only 4.75% to the overall population with subclinical hypothyroidism and to the outcome of the systematic review.

Meta-analysis

To assess whether subclinical hypothyroidism was associated with impairment of various cognitive domains, we analyzed MMSE separately as a measure of global cognition. Ten out of the 15 studies provided MMSE results either at baseline or at follow-up. The rest of the cognitive tests were categorized into tests of executive function or of memory, as shown in **Table 3**. Data from the 15 studies was pooled first for cross-sectional analysis, and meta-analyzed separately for global cognition (MMSE), executive function, and memory. The pooled ES for MMSE was −0.01 (95% CI −0.09, 0.08), with heterogeneity $(I)^2$ of 55.1% (**Figure 2A**). Pooled ES was <0.001 (95% CI −0.10, 0.09) for executive function ($I^2 = 13.5\%$) (**Figure 2B**), and 0.01 (95% CI −0.12, 0.14) for memory ($I^2 = 46.9\%$) (**Figure 2C**). These analyses indicated that available evidence does not support an association of subclinical hypothyroidism with worse performance in MMSE, executive function or global cognition.

Prospective analysis was done for MMSE in four studies from which prospective data was available (**Figure 3**). The pooled ES was 0.03 (95% CI −0.001–0.07) $P = 0.055$, with heterogeneity (I^2) of <0.001%. Thus, subclinical hypothyroidism was not significantly associated with accelerated decline of global cognition, as assessed by MMSE. Due to the small number of available studies, prospective analysis was not done for executive function or memory.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed on studies with similar TSH cut-off values, and in studies with similar study design (cross-sectional or prospective). The ES of these different subgroups were essentially similar, indicating that in this meta-analysis, subclinical hypothyroidism was not significantly associated with cognitive impairment.

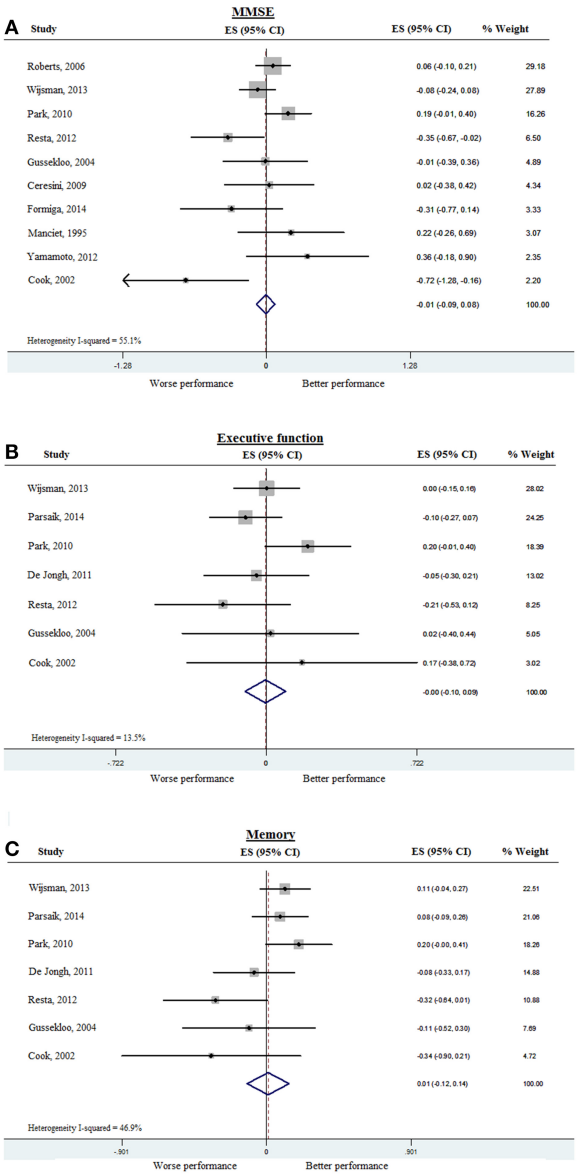

FIGURE 2 | Forest plots depicting the cross-sectional associations observed between subclinical hypothyroidism (compared to controls) and cognitive performance in 10 studies, arranged according to the weight of the studies. Data was pooled from cross-sectional studies and baseline data of prospective studies. **(A)** Association between subclinical hypothyroidism and global cognition as measured by MMSE, **(B)** Association between subclinical hypothyroidism and executive function, and **(C)** Association between subclinical hypothyroidism and memory. The pooled effect sizes are displayed as diamonds. MMSE, Mini-mental state examination.

Discussion

On the basis of the findings of this systematic review and meta-analysis we did not find evidence supporting an association of subclinical hypothyroidism with cognitive

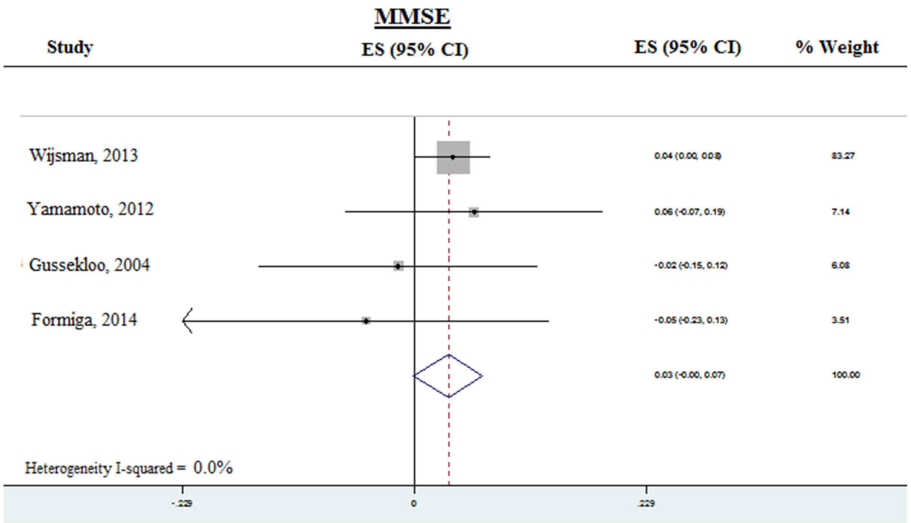

FIGURE 3 | Forest plots depicting the prospective analysis of associations observed between subclinical hypothyroidism and decline in global cognition as measured by MMSE, arranged according to the weight of the studies. The pooled effect sizes are displayed as diamonds. MMSE, Mini-mental state examination.

impairment in relatively healthy, community-dwelling elderly. Out of 15 observational studies, only two small cross-sectional studies (Cook et al., 2002; Resta et al., 2012) observed statistically significant associations between subclinical hypothyroidism and cognitive impairment, namely global cognition (MMSE), and memory. All other studies indicated a lack of association. No evidence was found that the lack of association between subclinical hypothyroidism and cognitive impairment was limited to unadjusted studies, or to studies of lower methodological quality. Meta-analysis of studies from which data for cross-sectional analysis could be retrieved, revealed lack of association between subclinical hypothyroidism and global cognition (assessed by MMSE) as well as lack of association of subclinical hypothyroidism with memory and executive function. Subgroup analyses by type of study design showed a similar trend in the prospective cohort studies group compared with the cross-sectional studies. We also did not find evidence supporting an association of subclinical hypothyroidism with cognitive impairment in a prospective analysis. However, the number of studies retrieved for prospective analysis was low and the study quality (assessed by scoring based on key indicators) varied.

Our results are in line with previous focused reviews (Parle et al., 2010; Joffe et al., 2013) supporting a lack of association between subclinical hypothyroidism and cognitive impairment that largely drew upon the results from large population based studies (Roberts et al., 2006). In contrast, another review conducted on the association between TSH and cognitive impairment in community dwelling and hospitalized elderly (Annerbo and Lökk, 2013) reported some evidence supporting the association between subclinical hypothyroidism and cognitive impairment, which was driven by studies showing an association between thyroid hormones and dementia. Thus, previous observational studies on the association of cognitive impairment and subclinical hypothyroidism have yielded conflicting results. Our finding of lack of association between subclinical hypothyroidism and cognitive impairment is also in line with the results of two placebo controlled randomized clinical trials (Jorde et al., 2006; Parle et al., 2010) that showed no effect of treatment with T4 on cognitive endpoints in participants with subclinical hypothyroidism.

To our knowledge, this is the first meta-analysis to examine the cross-sectional and prospective associations between subclinical hypothyroidism and cognitive impairment using available evidence. By pooling the data from the 15 studies, a total of 19,944 participants, of whom 1,199 had subclinical hypothyroidism were analyzed. This increased the power to detect potential associations and reduced the probability of false-negative results (Resta et al., 2012). Case-control and cross-sectional studies are more susceptible to bias, particularly selection bias for case-control studies (Hulley et al., 2001). Although bias cannot be excluded, almost all the cross-sectional studies that fulfilled our quality criteria demonstrated the absence of a statistically significant association between subclinical hypothyroidism and cognitive impairment (Hogervorst et al., 2008; Park et al., 2010).

Overt hypothyroidism has been associated with global cognitive impairment as well as with impairments in various cognitive domains, notably in memory and executive function. Because thyroid dysfunction can be seen as a continuum, it has been hypothesized that subclinical hypothyroidism might also be associated with mild cognitive impairment. The inverse physiological relationship between circulatory levels of TSH and thyroid hormones implies that in subclinical hypothyroidism, thyroid hormone action may be slightly reduced (even though circulatory thyroid hormones are still in the normal range),

which might be associated with subtle defects in specific cognitive domains, including memory and executive function. Moreover, one might speculate that potential associations between subclinical hypothyroidism and cognitive impairment are stronger when TSH is markedly increased (TSH > 10 mIU/L) as compared to mild or moderate increases. Similarly, it was found previously that associations between subclinical hypothyroidism and risk for coronary heart disease and mortality were strongest with a TSH concentration of 10 mIU/L or greater (Rodondi et al., 2010).

This analysis has four main limitations. Firstly, all data were obtained from observational studies, many of which are cross-sectional studies. There is a possibility of bias in the selection of included studies, bias and quality problems in the original studies, publication bias, heterogeneity, and confounding (Stroup et al., 2000). To limit bias in the selection of included studies, broad inclusion criteria were used for studies that provided quantitative data on the risk of cognitive impairment in elderly participants with subclinical hypothyroidism. Furthermore, sensitivity analyses were performed according to differences between the studies and methodological study quality, as recommended (Berlin, 1995; Stroup et al., 2000). Many of the original studies did not have statistically significant results, thus a meta-analysis was conducted to increase the power to find an association. Still, the negative conclusion of this systematic review and meta-analysis may be limited by inherent biases and differences in study designs (Huston and Naylor, 1996). However, the sensitivity analyses performed did not suggest that the presented results meaningfully depended on differences in study designs or other study characteristics.

Secondly, the possibility of misclassification of subjects as having subclinical hypothyroidism cannot be ruled out (Huston and Naylor, 1996). In most of the studies, the diagnosis of subclinical hypothyroidism was based on single assessment of TSH, without repeated confirmatory TSH measurement. This could have resulted in inclusion of individuals with only transiently elevated TSH levels. Furthermore, none of the included studies used age-adjusted TSH reference ranges to enroll the subjects. Since increased age has been associated with an increase in the upper limit of the TSH reference range (Zhu et al., 2006), the use of unadjusted reference ranges may have resulted in misclassification of some elderly participants as having subclinical hypothyroidism. This misclassification may have resulted in underestimation of the association between subclinical hypothyroidism and cognition. However, since the 95% CI around the estimates are quite narrow and the misclassification is likely to be small, a large effect of subclinical hypothyroidism on cognition can be confidently ruled out.

Thirdly, the definitions of subclinical hypothyroidism and cognitive decline were slightly different between the studies. The use of different TSH cut-offs reflects the absence of consensus to define subclinical hypothyroidism (Helfand, 2004; Surks et al., 2004). Some studies used a TSH upper limit of <4.5 mIU/L (Cook et al., 2002; Park et al., 2010), and the inclusion of those participants may have blunted the effect of any observed associations, since they may not have had subclinical hypothyroidism (Surks et al., 2004). However, the sensitivity analyses pooling more homogeneous studies gave similar results indicating a lack of evidence supporting an association of subclinical hypothyroidism with cognitive impairment. However, one might speculate that potential associations between subclinical hypothyroidism and cognitive impairment might only be present when TSH is markedly increased (TSH > 10 mIU/L). Future studies using individual participant data should be directed at analyzing available evidence for an association between subclinical hypothyroidism and cognition based on TSH categories, as was done previously for associations between subclinical hypothyroidism and coronary heart disease (Rodondi et al., 2010).

Fourthly, there were several differences in methodologies and choice of cognitive domains that were tested in the studies in this systematic review and meta-analysis. Thus, we cannot exclude the possibility that subclinical hypothyroidism might be associated with subtle defects in specific domains that can only be identified using highly specific cognitive tests and measures. Indeed, functional neuro-imaging studies in participants with subclinical hypothyroidism and markedly elevated TSH levels has revealed impairments in working memory and brain areas associated with executive function that reversed by treatment with T4 (Zhu et al., 2006). However, the clinical relevance of such specific measures remains unclear. Moreover, different laboratory methods were used for the measurements of TSH and fT4. In addition, TSH has a distinct circadian rhythm and time of the measurements of TSH was not reported in the articles, which may have affected the results.

In conclusion, this systematic review and meta-analysis provides no evidence that supports an association between subclinical hypothyroidism and cognitive impairment in relatively healthy, community dwelling elderly. However, available prospective studies were limited. Thus, additional large, high-quality studies are needed that will allow for more extended analyses.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2015.00150

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The acute effects of exercise on cortical excitation and psychosocial outcomes in men treated for prostate cancer: a randomized controlled trial

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Purpose: Regular exercise improves psychological well-being in men treated for prostate cancer (PCa). For this population and among cancer survivors in general, the effect of a single bout of exercise on self-report or objective measures of psychological well-being has not been examined. We examined the acute effect of a single bout of exercise on the cortical silent period (CSP) and on self-reported mood in men that have received treatment for PCa.

Methods: Thirty-six PCa survivors were randomly assigned to 60 min of low to moderate intensity exercise or to a control condition. Outcomes were assessed immediately before and after either the exercise or the control condition.

Results: No significant between-group differences were observed in CSP or mood were observed following the exercise session or control conditions. Participants with higher scores of trait anxiety had significantly shorter CSP at baseline, as well as those receiving androgen deprivation therapy. Age and baseline CSP had a low-moderate, but significant negative correlation. Changes in CSP following the exercise condition were strongly negatively correlated with changes in self-reported vigor.

Conclusion: While we did not observe any acute effect of exercise on the CSP in this population, the associations between CSP and trait anxiety, age, and vigor are novel findings requiring further examination.

Implications for Cancer Survivors: Exercise did not acutely affect our participants in measures of psychological well-being. Additional mechanisms to explain the chronic psychosocial benefits of exercise previously observed in men with PCa require further exploration.

Clinicaltrials.gov Identifier: NCT01715064 (http://clinicaltrials.gov/show/NCT01715064).

Keywords: cortical silent period, anxiety, depression, physical activity, prostate cancer, randomized controlled trial

INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer and the third leading cause of cancer-related death among Canadian men (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013). Fortunately, advances in detection and treatment have led to earlier diagnosis and treatment, improving 10-year survival rate to over 95 (Bill-Axelson et al., 2008). Accordingly, the population of PCa survivors is growing, but the survivorship period frequently remains fraught with treatment side effects including detriments to body composition and physical capacity, depression, anxiety, fatigue, and overall reductions in quality of life (Alibhai et al., 2006). Given that physical activity and exercise have demonstrated clinically relevant physical and psychosocial benefits for men with PCa, exercise has become vital to PCa management paradigms (Thorsen et al., 2008).

Most current research on exercise and PCa focuses on the psychosocial effects of routine exercise over several months. To

Abbreviations: ACSM, American College of Sports Medicine; ADT, androgen deprivation therapy; ANCOVA, analysis of covariance; APB, abductor pollicis brevis muscle; BOLD, blood oxygen level dependent; CONSORT, consolidated standard for reporting trials; CSP, cortical silent period; GABA, gamma-aminobutyric acid; EEG, electroencephalogram; M1, primary motor cortex; mm, millimeter; ms, milliseconds; PCa, prostate cancer; RCT, randomized controlled trial; s, seconds; SMA, supplementary motor area; TMS, transcranial magnetic stimulation.

date, the acute effects of exercise on psychosocial well-being in PCa patients have not been examined. In other clinical populations, single exercise bouts have improved mood, reduced depression/anxiety, and increased vigor (Hansen et al., 2001; Bartholomew et al., 2005; Peluso and Guerra de Andrade, 2005). It would be advantageous to better understand single-session effects in PCa, as programs of several months duration are composed of single bouts that may each produce important acute psychosocial benefits. Interestingly, most studies examining the exercise effects on psychosocial outcomes in PCa patients have assessed fatigue, health-related quality of life and various physical measures, whereas only a few have focused on anxiety (Carmack Taylor et al., 2006) and depression outcomes (Carmack Taylor et al., 2006; Culos-Reed et al., 2010). Furthermore, no studies have evaluated the effects of exercise on neurophysiological outcomes that may affect mood.

Our group has previously shown positive mood effects resulting from mindfulness meditation and cognitive behavioral therapy with the TMS protocol termed the CSP (Radhu et al., 2012; Guglietti et al., 2013). CSP is a non-invasive method of examining cortical inhibition of the primary motor cortex, reflecting mechanisms regulated by inhibitory GABA interneurons (del Rio and DeFelipe, 1997). The CSP is one of the most widely investigated measures of cortical inhibition, and is a quick, valid, and objective measure of how cortical physiology is implicated in psychological distress. Deficits in cortical inhibition have been observed in a range of psychiatric diagnoses such as major depressive disorder (Cryan and Kaupmann, 2005; Levinson et al., 2007), anxiety disorders (Cryan and Kaupmann, 2005), obsessive-compulsive disorder (Greenberg et al., 2000; Richter et al., 2012), schizophrenia (Daskalakis et al., 2008), and borderline personality disorder (Barnow et al., 2009).

The CSP represents the period of suppression of contralateral tonic electromyography (EMG) activity produced by cortical stimulation. Many studies report that CSP is related to the $GABA_B$ receptor-mediated inhibitory activity (Werhahn et al., 1999), especially when higher stimulation intensities are used (Paulus et al., 2008). Evidence supports the hypothesis that the early part of CSP (i.e., first 50 ms) is determined by spinal mechanisms, whereas the later part is mediated by cortical inhibition (Inghilleri et al., 1993; Chen et al., 1999). CSP lengthening is indicative of potentiation of $GABA_B$-mediated cortical inhibition and has been associated with reduced psychological stress (Cryan and Kaupmann, 2005), cognitive behavioral therapy (Radhu et al., 2012), mindfulness meditation (Guglietti et al., 2013), and antipsychotic medication (Liu et al., 2009). Given that the CSP is negatively correlated with mental distress and PCa patients are prone to chronic anxiety and depression, CSP may be altered in this population. Indeed, potentiation of $GABA_B$ mediated inhibitory neurotransmission, measured as lengthened CSP, may be associated with symptomatic improvement and mental well-being, and may reflect benefits the PCa patient experiences regarding anxiety or depression. Lengthened CSP has already been demonstrated with high-intensity exercise and linked to improved functional performance in Parkinson's disease; however, no psychosocial measures were recorded in this trial (Fisher et al., 2008).

Research indicates that age-related deteriorations in cortical inhibition are not necessarily pathological and may be due to normal aging. Outside of motor tasks, inhibitory control has been shown to require increased prefrontal activation measured using BOLD activity in order to compensate for the differences in older adults as compared to younger adults (Nielson et al., 2002). However, most of this research assumes that the typical markers for cortical inhibition related declines from aging are decreased reaction time and decreased motor coordination. In attention-demanding reaction time tasks that require $GABA_A$ pathways, EEG recordings from older adults exhibited stimulus-preceding negativity and attenuated contingent negative variation (Hillman et al., 2002) and stymied contingent negative variation amplitudes after the warning signal but preceding the imperative signal and execution of a motor task (Sterr and Dean, 2008). Furthermore, TMS applied to M1 during the waiting period demonstrated neural compensation by older individuals in order to achieve similar reaction times when compared to their younger counterparts, presumably by an increased recruitment of $GABA_A$ pathways (Fujiyama et al., 2012). Because the inhibition of M1 is predominantly controlled by prefrontal cortex/premotor regions, intracortical explanations for slowed reaction times due to aging are likely to be found in the aforementioned brain regions. This claim is further supported by Buch et al. (2010) and Neubert et al. (2010) who used diffusion-tensor imaging to show that specific structures that connect prefrontal cortex with M1 (central-prefrontal/premotor and pre-SMA, respectively) had deteriorated in proportion to the measured reductions in cortical inhibition.

Extending this theory of reduced cortical inhibition in the aging population to the field of exercise physiology can be found in the following studies on motor coordination in older adults. TMS studies on complex motor tasks of low coordination stability illustrate the recruitment of inhibitory processes (i.e., CSP) that are normally observed in younger adults but seem to be absent in older adults; participants who are able to register greater CSP measurements are the ones capable of successfully accomplishing the above mentioned motor tasks (non-isodirectional patterns with ipsilateral limbs; Siebner et al., 1998; Fujiyama et al., 2009). Motor coordination was shown to deteriorate in tasks of higher speeds, especially with regards to movement variability, phase wandering, and phase transitions. The authors suggested that this is likely modulated by $GABA_B$ pathways. However, this relationship between the practice of exercise gross motor tasks and with cortical inhibition particularly in older adults who are expected to have declines in this area remains unclear. Accordingly, the objectives of this study were to (1) examine the effects of a single bout of exercise on the CSP and self-report measures of mood in men who have been treated for PCa; and (2) assess the relationship between post-exercise changes in CSP and mood.

MATERIALS AND METHODS

STUDY DESIGN

This study was a prospective, RCT of a single bout of exercise versus a non-exercise (control) condition in PCa patients that have

received curative treatment for PCa. Concealed randomization was conducted using sequentially numbered opaque envelopes containing group assignments and was provided to participants following the baseline assessment. Training staff and participants were unblinded to group allocation; however, outcome assessors were blinded. The trial was approved by the research ethics review committees at participating institutions and all participants provided written informed consent prior to participation.

PARTICIPANTS

Eligible patients were approached for participation by a research coordinator following a urology clinic appointment at the Princess Margaret Cancer Centre in Toronto, ON, Canada from June to October, 2010. Patients could also respond to study information posters located in the clinic waiting areas. Patients were eligible if they: (i) had histologically confirmed PCa; (ii) were $\geq$6 months post-curative therapy for PCa (radical prostatectomy or radiation therapy) with or without adjuvant ADT; (iii) were willing and able to provide informed consent; (iv) if metastatic disease was present, they were physically asymptomatic (e.g., no bone pain); (v) had no contraindications to exercise; (vi) were between ages 45 and 85 years; (vii) were not diagnosed with psychotic, addictive, or major cognitive disorders or had a history of chronic usage of psychotropic medication (anti-depressants, anxiolytics, anti-psychotics, benzodiazepines, etc.); (viii) had no contraindications to magnetic exposure; (ix) had no prior history of seizures or diagnosis of epilepsy; and (x) were right-hand dominant.

A priori, we calculated the sample size necessary to detect a significant, clinically important difference in CSP over time (Group $\times$ Time interaction effect, F statistic) between the exercise and control groups. The parameters of this calculation were as follows: estimated effect size $= 0.25$, $p < 0.05$, power $= 0.80$, required sample: $N = 36$ ($n = 18$ per group).

TREATMENT GROUPS

Exercise group

Participants in the exercise group each received an identical 60-min low to moderate intensity exercise routine conducted at the hospital gymnasium. A certified personal trainer under the supervision of a certified exercise physiologist guided the sessions. Exercise sessions consisted of 5 min of light, callisthenic warm-up and stretching, 25 min of low-impact aerobics, 25 min of resistance training, and a 5-min cool-down including light stretches. The aerobic exercise was conducted using a low-impact, step-aerobic video to standardize the activities. Participants were evaluated during the exercise session using a heart rate monitor to maintain the prescribed aerobic intensity of 40–60% of heart rate reserve. The resistance training consisted of five exercises performed at an intensity of 8–12 repetition maximum, and included: seated row, squat, chest press, shoulder press, and abdominal crunches on a stability ball.

Control group

Participants in the control group were required to sit quietly in front of a computer monitor where they watched 60 min of emotionally neutral television programming, consisting of 6 min $\times$ 10 min episodes of Walt Disney's Silly Symphony Cartoons [these programs have been previously used for inciting neutral neurological stimulus, i.e., neurological rest (Guglietti et al., 2013)]. Participants allocated to the control group were offered an exercise session similar to the exercise group following the study.

ASSESSMENTS

Participants completed two outcome measure assessments: before randomization (T1) and immediately after their intervention or control assignment (T2). At both time points, participants completed a package of questionnaires and TMS for CSP.

OUTCOMES

The primary outcome of this study was the duration of the CSP. TMS was applied to the hand area of the left motor cortex with a figure-of-eight magnetic coil and two Magstim 200 magnetic stimulators (Magstim, Whitland, Dyfed, Wales). The coil diameter was 70 mm for each loop. The coil was held tangentially on the head with the handle pointing backward and 45° laterally from the midline. Surface electromyographic recordings of the right APB were collected using dedicated software (Cambridge Electronics Design, UK), using disposable disk electrodes placed in a tendon-belly arrangement over the bulk of the muscle. Subjects were asked to maintain relaxation throughout the experiments and the EMG was monitored on a computer screen and via speakers at high gain. Each TMS session consisted of the establishment of the participant's resting motor threshold of the right APB, followed by the CSP paradigm. TMS testing was conducted by a blinded technician, trained and experienced in TMS and CSP testing. Measurement of the contralateral CSP duration was obtained in moderately tonically active right APB (i.e., 20% of maximum contraction) by stimulating the left motor cortex with intensities of 140% of resting motor threshold. This intensity was chosen based on evidence that suggests that CSP duration at the higher stimulus intensities (140% of motor threshold) mainly reflects the activation of $GABA_B$ receptor-mediated inhibitory neurotransmission (Chamberlain et al., 2006). Ten trials were performed. The CSP duration was the time from the motor evoked potential onset to the return of any voluntary EMG activity. This is referred to as the absolute CSP and ends with a deflection in the EMG waveform (Tergau et al., 1999). The CSP was determined with a previously published automated method (Daskalakis et al., 2008).

Several self-report measures of mood were implemented to further assess acute exercise-related responses. The Exercise-Induced Feeling Inventory (EIFI; Gauvin and Rejeski, 1993) is a 12-item measure that assesses acute exercise-related feelings using four subscales: positive engagement, revitalization, tranquility, and physical exhaustion. The EIFI demonstrated strong internal consistency and reliability coefficients (Gauvin and Rejeski, 1993). The Profile of Mood States-Short Form (POMS; Shacham, 1983) assesses mood based on six factor-based subscales, derived from the original scale (McNair et al., 1971): tension–anxiety, depression–dejection, anger–hostility, fatigue–inertia, vigor–activity, and confusion–bewilderment with a seventh score of Total Mood Disturbance (calculated by subtracting the score on the one positively

scored subscale, vigor–activity, from the sum of the other five subscales; McNair et al., 1971). The short form version is highly correlated across all subscales with the original, long-version (Schoenfeld et al., 2013). The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983) is a brief, 40-item self-report assessment of state and trait anxiety in adults. This measure is reliable and valid, and concordance with other measures of anxiety (Peterson and Heilbronner, 1987). To assess depression and anxiety we used the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). Construct validity was demonstrated by the two scales correlating well with psychiatric clinical interview ratings (depression, $r = 0.70$ and anxiety, $r = 0.74$, $p < 0.001$) and by responsiveness to a counseling intervention (Johnston et al., 2000).

Demographics (e.g., age, educational status, etc.) and other information believed to have a possible influence on outcomes (tumor and treatment characteristics) were collected and compared across treatment conditions. Baseline physical activity volume was measured to assess its relationship with baseline CSP. Physical activity volume was measured using the Godin Leisure-Time Exercise Questionnaire (Godin and Shephard, 1985) which is a 3-item measure that assesses the frequency of mild, moderate and strenuous bouts of exercise performed for at least 15 min in duration during a typical week. The Godin Leisure-Time Exercise Questionnaire has been successfully used in exercise studies with PCa survivors (Culos-Reed et al., 2010), and an independent evaluation confirmed its reliability/validity compared to nine other self-report measures of exercise (Jacobs et al., 1993).

STATISTICAL ANALYSIS

Baseline between-group comparisons were performed using independent samples *t*-test for continuous variables and chi-squared analyses for categorical variables. For the primary and secondary outcomes, ANCOVA were conducted to compare differences in CSP and questionnaire data at post-intervention between-groups (exercise versus control), controlling for the baseline value of the outcome of interest. Pearson correlation coefficients were used to assess the relationship between self-reported mood and age with CSP at baseline. Pearson correlation coefficients were also conducted for T1–T2 difference (change score) in self-reported mood and CSP for the exercise and control groups. We conducted two exploratory analyses. First, we assessed the effect of meeting the ACSM physical activity guidelines for cancer survivors (150 min of moderate intensity exercise per week) on CSP (baseline value) using independent samples *t*-test. Second, we assessed the effect of ADT on CSP (baseline value) using independent samples *t*-test. Data were analyzed using the Statistical Package for Social Sciences version 19.0 (IBM, Armonk, NY, USA).

RESULTS

The CONSORT diagram is presented in **Figure 1**. Eighty-six eligible participants were approached for participation and 19 agreed (22% participation rate). Seventeen participants responded to the study poster. The 36 participants were randomly assigned to the exercise ($n = 18$) or control ($n = 18$) group.

Baseline participant characteristics are presented in **Table 1**. The exercise and control groups were different at baseline in age [exercise: 67.7 years ($\pm$7.6) versus control: 61.6 years ($\pm$9.1); $p = 0.04$]. The groups were similar in all demographic measures, treatment characteristics, and outcome measures ($p > 0.05$). There were no adverse health events related to the exercise or TMS procedures.

The effect of the exercise session on primary and secondary outcomes is presented in **Table 2**. There were no significant main effects for group or time, and no significant interaction effects for any of the group comparisons. There was a trend toward reduced tension ($F_{(1,32)} = 3.885$; $p = 0.057$) and increased positive engagement ($F_{(1,32)} = 2.967$; $p = 0.095$) in the exercise group compared to the control group.

Given the observed baseline between-group differences in age, we conducted a secondary analysis with age as a covariate in the ANCOVA. There was a trend toward increased positive engagement in the exercise group compared to the control group ($F_{(1,31)} = 2.928$; $p = 0.097$). There were no significant findings for our other outcomes ($p < 0.05$).

A statistically significant positive correlation was observed between CSP and the trait anxiety subscale of the STAI at baseline ($r = 0.48$, $p = 0.004$; i.e., longer CSP was associated with increased anxiety). Age and CSP shared a significant, low-moderate negative correlation ($r = -0.34$, $p = 0.041$). There were no other significant correlations at baseline. In the exercise group, there was a strong, negative correlation between the change-scores of CSP and the vigor subscale of the Profile of Mood States ($r = -0.714$, $p = 0.006$). There were no other significant correlations in the exercise or control groups.

Thirty participants met the ACSM's physical activity guidelines with no difference in the frequency of those meeting or not meeting the guidelines in the exercise and control groups ($\chi^2 = 3.2$, $p = 0.074$). There was no difference in baseline CSP between those meeting the guidelines and those that did not [meeting guidelines: 0.108 s ($\pm$0.028) versus not meeting guidelines: 0.107 s ($\pm$0.018); $p = 0.975$].

Fourteen participants were currently receiving ADT. Participants receiving ADT had a significantly shorter CSP than participants not receiving ADT [on-ADT: 0.961 s ($\pm$0.029) versus off-ADT: 0.115 s ($\pm$0.023); $p = 0.035$]. In bivariate correlational analyses restricted to participants that were not receiving ADT, CSP was positively correlated with the trait anxiety subscale of the STAI ($r = 0.543$, $p = 0.011$). There were no other significant (i.e., $p < 0.05$) bivariate correlations. When completing the ANCOVAs of the effect of exercise versus controls on CSP in participants who were off ADT ($n = 22$), there was no significant interaction effect of exercise on CSP ($F_{(1,19)} = 0.157$, $p = 0.697$), while the main effect of the group was related to baseline differences in CSP ($F_{(1,19)} = 11.75$, $p = 0.003$).

DISCUSSION

To our knowledge, this is the first study to assess the acute psychological and neurophysiological effects of exercise in a population of cancer survivors. While, Fisher et al. (2008) previously demonstrated lengthened CSP with high-intensity exercise training in participants with Parkinsons's disease, ours was the first

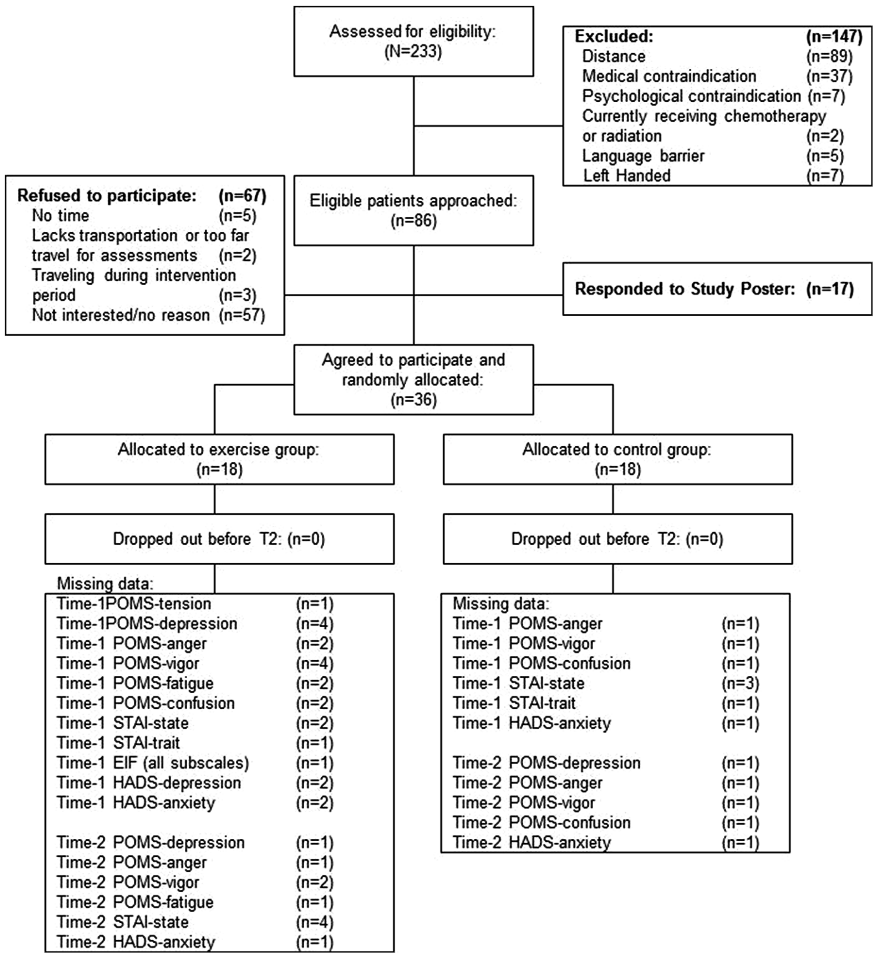

FIGURE 1 | CONSORT diagram.

assessment of exercise effects, CSP, and mood in a single study. Fisher et al. (2008) found functional improvements in patients with Parkinson's disease of gait speed, step and stride length, and hip-ankle joint excursion and improved weight distribution during sit-to-stand tasks, but they did not assess mood. Our study found that one acute bout of exercise did not alter CSP in PCa survivors whereas the CSP lengthening effects demonstrated by Fisher et al. (2008) required 24 high-intensity exercise sessions over 8 weeks. Accordingly, it may be that exercise-related CSP effects, if they occur reliably, require more extensive, consistent training than a single bout. Further research is warranted regarding the CSP effects of exercise as recent animal studies suggest anxiety-reducing exercise effects linked to the same GABAergic responses monitored through CSP (Schoenfeld et al., 2013).

Novel acute relationships between CSP and psychological measures were observed, namely a positive correlation between CSP and trait anxiety. The relationship between CSP and trait anxiety may be characteristic of a group of patients with a history of PCa, in their seventh; and several were actively androgen deprived ($n = 14$), a treatment often used for patients with advanced disease. Consequently, this group may have chronic elevations in anxiety but with a longer CSP as a result of adapting to life with routine monitoring for disease progression and high risks of receiving terminal disease prognoses. The longer CSP may be associated with greater neuroinhibition, and in contrast with the greater levels of neuroexcitation, likely associated with more impulsive behavioral-response styles. Those survivors who are more reflective might be more realistic about heightened mortality risk and therefore more accustomed to living with mortality anxiety as a regular feature of current lifestyle. Conversely, CSP was not related to state anxiety, a measure of more immediate (situational) anxiety, further suggesting that these men were chronically anxious, not situationally anxious. Notwithstanding these intriguing relationships, cautious interpretation of these correlative findings is warranted given that they were secondary analyses of a relatively small sample and the number of correlational analyses increases the risk for Type 1 error.

We observed no effect of meeting the ACSM guidelines of physical activity on CSP, suggesting that CSP may not be a marker for chronic adherence to an exercise program at the level prescribed by ACSM. CSP was significantly shorter in men that were treated with

Table 1 | Demographic characteristics of study participants.

	Exercise (n = 18)	Control (n = 18)	p-value
Age (years)	67.7 (7.6)	61.6 (9.1)	0.035
Physical activity volume (min/week)	362.1 (315.4)	420.6 (249.5)	0.541
Ethnicity			
Caucasian	16 (88%)	15 (83%)	0.192
South East Asian/East Asian	0	3 (17%)	
African–Canadian	1 (6%)	0	
Other	1 (6%)	0	
Marital status			
Married	12 (67%)	13 (72%)	0.814
Single (including widowed, separated, divorced)	6 (33%)	5 (28%)	
Annual income			
<$40k	4 (22%)	4 (22%)	0.394
$40–$80k	6 (33%)	3 (17%)	
>$80k	8 (44%)	10 (61%)	
Education			
Less than high-school	1 (5%)	0	0.275
High-school degree	6 (33%)	2 (11%)	
College/trade school	3 (17%)	1 (5%)	
University degree	3 (17%)	6 (33%)	
Graduate degree	4 (23%)	8 (46%)	
Other	1 (5%)	1 (5%)	
Employment			
Retired	9 (50%)	5 (28%)	0.131
Working part time	4 (22%)	2 (11%)	
Working full time	5 (28%)	11 (61%)	
Currently smokes tobacco	6 (33%)	4 (22%)	0.392
Primary cancer treatment			
Radical prostatectomy	12 (67%)	14 (78%)	0.730
External beam radiation	4 (22%)	3 (17%)	
Androgen deprivation therapy	2 (11%)	1 (5%)	
Currently receiving androgen deprivation therapy	9 (50%)	5 (28%)	0.171

Data on continuous variables are presented as Mean (SD); p-value for between-group differences of continuous variables using independent sample t-test. Data for categorical variables are presented as Frequency (% of group); p-value for χ^2.

ADT than those who were not, a finding that contributes to the uncertainty of findings in previous research on the role of testosterone on cortical excitability and inhibition. In a study by Bitran et al. (1993), testosterone exposure was found to be associated with increased anxiolytic behavior as well as inhibition via GABAergic pathways in rats. By extension, a *decrease* in testosterone via ADT would be expected to inhibit these same GABAergic pathways, leading to a disinhibited level of cortical excitability. Consistent with this, our findings suggest that ADT may lead to a decreased cortical inhibition as evidenced by the significantly shortened CSP in men that were treated with ADT compared to those that were not. This result contributes evidence addressing the controversial topic of whether testosterone is associated with cortical excitation (Bonifazi et al., 2004) or inhibition (Bitran et al., 1993; Herzog et al., 1998).

Finally, we found a negative correlation between changes in CSP and vigor in the exercise group only (longer CSP correlated with reduced vigor) which may indicate that the men who had exercised most vigorously for their capacities (therefore lengthening CSP) were most fatigued at the post-exercise data point (about 15 min after the exercise bout concluded). The invigorating effect that might be associated with more long-term commitment to exercise may not have appeared yet for these men.

Our study has methodological strengths. First, it was an RCT adequately powered to detect changes in CSP between the control and exercise groups. Second, our CSP assessors were blinded to

Table 2 | Acute effects of exercise on CSP and psychosocial outcomes.

	Δ(T2–T1)		Between-groups difference in mean change from T1 to T2	
Variable	**Exercise**	**Control**	***F***	***p***
CSP (sec)	0.001 (0.025)	0.006 (0.019)	1.222	0.277
STAI-state	0.36 (4.31)	1.07 (2.87)	0.205	0.655
STAI-trait	–0.29 (3.37)	1.06 (5.45)	0.538	0.469
POMS-tension	–2.71 (3.27)	–1.72 (2.14)	3.885	0.057
POMS-depression	–0.50 (2.84)	–0.94 (1.78)	1.569	0.375
POMS-anger	–1.47 (1.64)	–1.88 (2.45)	0.192	0.664
POMS-vigor	0.23 (3.81)	–0.59 (4.49)	0.241	0.627
POMS-fatigue	–0.84 (2.93)	–0.78 (2.41)	0.131	0.720
POMS-confusion	–1.56 (3.20)	–0.82 (1.24)	0.920	0.345
EIFI-positive engagement	1.35 (2.29)	–0.39 (3.91)	2.967	0.095
EIFI-revitalization	1.76 (4.07)	0.57 (3.36)	1.662	0.207
EIFI-tranquility	0.88 (1.90)	0.50 (3.13)	0.535	0.470
EIFI-exhaustion	0.76 (2.39)	–0.17 (2.30)	1.477	0.233
HADS-anxiety	0.44 (1.41)	0.18 (1.01)	0.105	0.748
HADS-depression	0.81 (2.73)	0.33 (1.92)	0.375	0.545

Data are presented as mean (standard deviation); Between-groups analysis: p-value reported for ANCOVA when adjusting for baseline value. CSP, cortical silent period; EIFI, Exercise-Induced Feeling Inventory; HADS, Hospital Anxiety and Depression Scale; POMS, Profile of Mood States – Short Form; STAI, State-Trait Anxiety Inventory; T1, Time Point 1 (baseline); T2, Time Point 2 (post-test).

group assignment. Third, we standardized exercise activity using an aerobic exercise video and resistance training routine that had strict parameters for training volume (repetitions, sets, heart rate, etc.). Fourth, we utilized both objective and subjective validated measures of psychological well-being. In particular, use of objective measures of cortical physiology believed to be significantly associated with psychological status can circumvent some response biases (placebo effect, social desirability, recall bias) confounding self-report measures.

Our study must also be considered in light of several limitations. First, we observed a between-group difference in age despite randomization; however, we adjusted for these differences in a secondary analysis that did not yield significant differences with the unadjusted model. The findings that CSP was not significantly increased with exercise could be explained by the characteristics of the aging motor cortex during physically complicated tasks, but a larger sample size of participants may be necessary in future research to detect a significant difference. Inclusion of a young adult control group may be advised. Further to the point on how aging affects CSP in a way that could potentially interact with the effects of exercise, researchers have previously shown that CSP relates with age. CSP was shown to differ in participants who had a 45 year gap (26 versus 71 years; Oliviero et al., 2006). In contrast, our participants are approximately 6 years apart in age. Further research is required on age-related changes in CSP.

A second limitation is that we did not control or measure the amount of time between the CSP measurements and the exercise or control activities. The exercise room was in an adjacent building, an approximately 5-min walk from the CSP measurement room, compared to the video-watching room which was on the same floor as the CSP measurement room. While no studies have examined any possible post-exercise declines of exercise-related effects on CSP, future studies should measure and control for the amount of time between exercise cessation and CSP measurement. However, in our study the post-test CSP was measured between 5 and 15 min after the intervention or control condition. Third, we included participants that were and were not actively undergoing ADT for PCa. While ADT was associated with a shorter CSP, we did not observe any effect of exercise-related to ADT status and the sample sizes of these sub-analyses were too small to be conclusive. Fourth, the low to moderate intensity of our exercise program may not have been sufficiently intense to stimulate significant changes in CSP. Previous measures of exercise on brain activity have demonstrated potential intensity-related differences (Nybo and Nielsen, 2001; Kamijo et al., 2004). Future studies should examine more intense training protocols for possible effects on CSP. Fifth, although we screened medical records and inquired about mental health history and treatments prior to participation, our screening of cognitive states may have been improved with the use of brief, validated measures such as the Mini-Mental State Examination (Folstein et al., 1975), and is recommended for future trials. Moreover, we excluded men who were using of anxiolytic and antidepressive medications as proxies for the presence of mood disorders, but did not confirm the absence of any psychopathology with a formal psychological assessment. Future trials would benefit from a formal evaluation of psychological states to reduce the possibility of confounding outcomes. Finally, we did not collect body composition measurements (e.g., height, weight) that at present do not appear to have a direct effect on CSP or post-exercise mood; however, they may have an indirect effect whereby the effort required to complete exercise is distinctly different in overweight or obese participants compared to healthy weight participants.

With previous studies in other populations suggesting that improvements in depression and anxiety could be attained with physical exercise and meditation, we hypothesized that one bout of acute exercise would be able to evoke similar responses in men with PCa and concomitant increases in CSP. Given that we did not find effects of acute, low to moderate exercise on CSP or anxiety and depression, it may be that longer, more frequent, or more intense sessions are required to induce changes in measures of cortical inhibition, especially those related to longer-acting mechanisms, such as CSP. More research in this field is required to clarify the role of exercise on the CSP.

AUTHOR CONTRIBUTIONS

Daniel Santa Mina: study conception, principal investigator, primary writer; Crissa L. Guglietti: study conception, outcome assessor, statistical analyses; Danilo R. de Jesus: participant screening, safety monitoring during TMS and CSP, secondary writer;

Saam Azargive: participant recruitment, intervention delivery support, secondary writer; Andrew G. Matthew: participant recruitment, final approval of manuscript, critical for intellectual content; Shabbir M. H. Alibhai: participant recruitment, final approval of manuscript, critical for intellectual content; John Trachtenberg: participant recruitment, final approval of manuscript, critical for intellectual content; Jeffrey Z. Daskalakis: study conception, critical for intellectual content, laboratory usage, final approval of manuscript; Paul Ritvo: study conception, critical for intellectual content, final approval of manuscript.

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Perceived Risk of Mental Health Problems in Primary Care

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In the face of limited resources and an aging population with increasingly care needs, healthcare systems must identify community-dwelling older adults with mental health problems at higher risk of adverse outcomes such as institutionalization, hospitalization and death, in order to deliver timely and efficient care. The objectives of this study were to assess the prevalence of mental health concerns and the associated perceived risk of adverse outcomes in a large sample of older patients in primary care (PC). We trained general practitioners and nurses to use the Risk Instrument for Screening in the Community to rank perceived risk of mental health concerns (including neurocognitive and mood disorders) from 1 (mild) to 3 (severe). The mean age of the 4499 people assessed was 76.3 years (SD = 7.3) and 2645 (58.8%) were female. According to the PC team 1616 (35.9%) were perceived to have mental health concerns of whom 847 (52.4%) were mild, 559 (34.6%) were moderate and 210 (13%) were severe. Patients with mental health concerns had higher odds of perceived risk of adverse outcomes (OR = 2.22, 95% CI 1.83–2.69 for institutionalization; OR = 1.66, 95% CI 1.41–1.94 for hospitalization; OR = 1.69, 95% CI 1.42–2.01 for death). These results suggest a high prevalence of mental health concerns among older adults and supports the need for early identification of patients at high-risk of adverse healthcare outcomes.

Keywords: risk, primary care, old people, mental health, RISC

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INTRODUCTION

There is growing recognition of the need to develop inclusive health service policies to integrate and track mental health issues. Previously surrounded by misconceptions and stigma, the importance of good mental health is now widely accepted. Reasons to promote the integration of mental health issues into primary care (PC) include: "(1) The burden of mental disorders is great; (2) Mental and physical health problems are interwoven; (3) The treatment gap for mental disorders is enormous; (4) PC for mental health enhances access; (5) PC for mental health promotes respect of human rights; (6) PC for mental health is affordable and cost-effective; (7) PC for mental health generates good health outcomes" (WHO and WONCA, 2008). More recently, the World Health Assembly recognized the extent to which mental and neurological disorders including Alzheimer's disease can cause morbidity and subsequent disability (WHA, 2012).

Mental health disorders including neurocognitive disorders affect approximately 165 million (38.2%) people in the European Union (EU), with no substantial cultural or country variations

for most conditions (Wittchen et al., 2011). Mental health disorders contribute to 26.6% of the total burden of disease [disability adjusted life years (DALY)] in Europe (Wittchen et al., 2011). Recognizing the differences between study methods, the lifetime prevalence of mental health problems may still be as high as 57%, particularly in lower socioeconomic groups (Rabins et al., 1996). Excluding dementia, the prevalence of psychiatric disorders is estimated at 16.3%, potentially rising to 21.6% by the year 2030 (Jeste et al., 1998). Psychiatric disorders are underestimated because of cognitive impairment, physical disorders, ageism or because older people attribute feeling depressed to old age itself and are discouraged from seeking help or reporting symptoms (Sarkisian et al., 2003). Others have subclinical disorders that do not meet the diagnostic criteria for psychiatric disorders but require attention (Xavier et al., 2013), contributing significantly to morbidity and mortality (Gallo et al., 1997; Steffens et al., 2000). The prevalence of these disorders approaches 33% in people 70 years and over (the Berlin Aging Study) (Helmchen et al., 1999). In Portugal, the annual prevalence of mental disorders is 22.9%, with 7.3% reported as mild, 11.6% as moderate and 4% as severe (Caldas de Almeida and Xavier, 2013). The Portuguese National Inquiry on Health (INE, 2009) showed that there is a high prevalence of probable psychological distress in older people that varies from 40.6% in people aged 65–74 years to 42.2% in those aged 75–84 years, reducing to 36.3% by 85 years. The percentage of women with psychological suffering is higher than for man, affecting half of older Portuguese women. These data are in line with international comparative studies that show that Portugal ranks high compared to other nations (Caldas de Almeida and Xavier, 2013).

Mental and physical health problems are often interwoven, particularly in older people (WHO and WFMH, 2010). The bidirectional negative impact of physical disease and depression may result in further disability (Menchetti et al., 2001) and is independently associated with an increased risk of mortality (Ganguli et al., 2002).

In high-income countries between 35 and 50% of people receive insufficient treatment (WHA, 2012), often due to under-detection and/or inadequate access resulting in a large treatment gap for mental disorders. Utilizing PC resources is crucial to overcome this, particularly in Portugal where 17% of patients with mental health problems seek help in PC compared to 11% in other EU countries (EC, 2010). Training health professionals to recognize mental health concerns by providing them with efficient and effective instruments is a first step to insure that older people can get proper treatment for their condition (WHA, 2012). Four theoretical models of managing mental health disorders in PC include: training; consultation-liaison; collaborative care, and replacement/referral (Bower and Gilbody, 2005). The training of PC professionals to identify and manage risk factors seems most appropriate.

Another important component is to support patients with mental health disorders in their home environment by supporting their caregivers or social network. Caregivers (mainly family) are considered the backbone of long-term care systems (OECD, 2013). The positive effect of an informal carer is well-recognized in mental health, particularly where the caregiver assumes the role of confident. On the other hand, caregiver strain or burden increases the risk of adverse healthcare outcomes (Paúl and Martin, 2003; Carretero et al., 2009). The number of people aged 50 or more years reporting to be caregivers in 2010 was 15.6% with 62.3% being women and 87% providing care on a daily basis (OECD, 2013). In Portugal, as in most of the southern European countries, there is a strong culture of family providing care for their older relatives, mainly supported by women (Lopes, 2013).

Given the importance of integrating mental health services into PC by efficiently and effectively screening and triaging patients with mental health disorders, this paper aims to: (i) establish the point prevalence of mental health concerns among community-dwelling older adults in PC in northern Portugal, (ii) identify predictive factors associated with mental health concerns, and (iii) determine the extent that mental health concerns affect patients perceived risk of three adverse healthcare outcomes: institutionalization, hospitalization and death as perceived by healthcare professionals working in the community using a new, short, global subjective risk prediction instrument called the Risk Instrument for Screening in the Community (RISC; O'Caoimh et al., 2014, 2015c).

MATERIALS AND METHODS

Study Design

This paper presents cross sectional data from a large, on going, prospective cohort study on mental health in northern Portugal. The project was approved by the ethics committee of the Regional Association of Health North (ARS North) and by each of the 24 Associations of Health Centers in the region where data was collected.

Participants

The sample comprises 4499 consecutive patients attending 29 PC practices who met the following inclusion criteria: (i) aged $> = 65$ years-old; (ii) living in the community; (iii) PC patients; (iv) living in the area covered by the ARS North; (v) provided informed consent. The exclusion criteria included patients aged less than 65 years, those deemed to be actively dying, including those receiving palliative care, and those already in institutional care, i.e., nursing home residents. Those not attending the PC center regularly, i.e., those lost to regular follow-up/attendance were also excluded as no accurate demographic data were available and they could not be scored with the RISC.

Measures

The RISC is a short (2–5 min), reliable (O'Caoimh et al., 2012, 2014) and valid global subjective assessment of risk. It has good internal consistency (O'Caoimh et al., 2015b,c). It is used as a pre-screen stratifying patients according to their risk level and is scored with a five point Likert scale from 1 to 5, where 1 is the lowest risk and 5 is the highest of three adverse health care outcomes (institutionalization, hospitalization, and

death) at 1 year from assessment. Each outcome is scored separately. The RISC also collects demographic data and scores the ability of the caregiver network (both formal and informal) to manage risk across three domains: the patients' Mental State, ADL State and Medical State, which can be used to inform the subjective assessment. The caregiver network score is again presented as a five point Likert scale, scored from 1 (can manage all risks) to 5 (the caregiver network is a liability or is absent). Risk is determined by a subjective assessment based upon the information gathered such that: risk equates to the severity of the concern minus the protective effect of the caregiver network for each of the three domains. The RISC is available at http://www.biomedcentral.com/1471-2318/14/104/figure/F1. Patients can be grouped into minimum (RISC scores 1 and 2) and maximum-risk (RISC scores 3–5) to facilitate analysis.

The RISC was developed in University College Cork (UCC), Ireland, as part the Community Assessment of Risk Treatment and Strategies (CARTS) program, a component of Irelands successful three star reference site application under the European Innovation Partnership on Active and Healthy Ageing (Sweeney et al., 2013; O'Caoimh et al., 2015d). The RISC was initially validated in Ireland against the Clinical Frailty Scale (CFS; Rockwood et al., 2005), an established frailty instrument, in 803 community dwelling older adults, aged over 65 years (O'Caoimh et al., 2014, 2015c; Leahy-Warren et al., 2015). Public health nurses scored the RISC and CFS for each patient and independent investigators, blind to the RISC score, followed up individual outcomes at 1 year. Those classified as maximum-risk were significantly more likely to experience all three outcomes (institutionalization, hospitalization, and death) at 1 year. The RISC had greater accuracy compared with the CFS, albeit it was a non-significant difference. The RISC better predicted institutionalization and death than hospitalization. A recent systematic review of risk-prediction instruments in the community confirmed that the risk compares favorably with similar tools, all of which have poor accuracy in predicting hospitalization (O'Caoimh et al., 2015a).

Procedures

The RISC was firstly translated from English into Portuguese by a committee of three experts in gerontology, all fluent in English. The Portuguese version of the RISC was then back translated into English. To ensure semantic equivalence and acceptability, this process was performed by a professional English translator and by a professional with experience in gerontology. The draft version was discussed with the team of authors and some minor changes were made. The instrument was piloted by a group of five healthcare professionals to ensure comprehensibility and no further changes were introduced.

Healthcare professionals, general practitioners (GPs) and practice nurses who agreed to participate, received 4 h of training and certification in scoring the RISC, delivered by the Portuguese research team that had itself received a 2-day training session from the authors of the RISC in UCC, Ireland. RISC training introduces the concept of risk and adverse outcomes; it discusses the main areas of concern (mental, functional, and medical), its relevance for the assessment, its contents and scoring instructions. RISC training is shown to increase inter-rater reliability (O'Caoimh et al., 2012). Once trained, GPs and a small number of practice nurses scored the RISC on their own patients only, using their clinical knowledge of each patient's current health status.

Statistical Analysis

Descriptive statistics were used to characterize the sample. Potential predictive factors relating to mental health concerns were tested using univariable logistic regression models. Considering covariates statistically significant in univariable models, a multivariable logistic regression model was performed.

Additionally, the effect of the presence/absence of mental health concerns, the severity and the ability of the caregiver network were tested as potential predictive factors of the risk of each adverse outcome (institutionalization, hospitalization, and death) in three distinct multivariable logistic regression models (adjusting for age, gender, ADL and medical concerns). The Akaike information criterion (AIC) were obtained to compare non-nested logistic models. In order to evaluate the discriminant capacity of each model, the area under the curve (AUC) obtained from receiver operator characteristic (ROC) curves was used. Comparisons of ROC curves for the same adverse outcome

TABLE 1 | Characteristics of the sample.

	n	%
Gender		
Male	1854	41.2
Female	2645	58.8
Age in years [mean(SD)]	76.3 (7.3)	
Living alone		
Yes	734	16.7
No	3653	83.3
Mental health concerns		
No	2883	64.1
Yes	1616	35.9
Severity		
Mild	847	52.4
Moderate	559	34.6
Severe	210	13.0
Caregivers ability to manage mental health concerns		
Can manage	783	48.5
Carer strain	531	32.9
Some gaps	221	13.7
Cannot manage	81	5.0
Absent/liability	0	0.0
ADLs concerns		
No	2456	54.6
Yes	2043	45.4
Medical concerns		
No	977	21.7
Yes	3222	78.3

were performed considering a proposed approach (Hanley and McNeil, 1983). The significance level was set at 0.05 for all analysis.

RESULTS

The sample comprises 4499 patients with a mean age of 76.3, standard deviation (SD) of 7.3 years, range 65–103 years. Of these 1854 (41.2%) were male and 2645 (58.8%) female. Only 734 patients (16.7%) were living alone. In total, 1616 (35.9%) of the patients were scored as having mental health concerns using the RISC, 2043 (45.4%) with ADL concerns and 3222 (78.3%) with medical concerns. Of patients registering mental health concerns on the RISC, less than half (48.5%) had a caregiver network that was perceived to be able to manage the situation. Option five of the care network (absence/liability) was not considered in the analysis because of the absence of records (**Table 1**). Evaluating the risk of adverse outcomes showed that 16.3% of the sample were perceived to be at risk of institutionalization, 32.8% at risk of hospitalization and 23.1% at risk of death.

Predictive Factors of Mental Health Concerns

In order to identify potential predictive factors of mental health concerns, univariable logistic regression models were performed. Results are shown in **Table 2**. Females had greater odds of mental health concerns [odds ratio (OR) = 1.26, 95% confidence interval (CI) 1.11–1.43] compared with males. Patients with either ADL concerns (OR = 10.1, 95% CI 8.76–11.7) or medical concerns (OR = 6.01, 95% CI 4.88–7.44) also had greater odds of having mental health concerns. Increasing age increased the risk of having mental health concerns (OR = 1.08, 95% CI 1.07–1.09) while living arrangement was not related to mental health concerns.

Considering significant factors of mental health concerns obtained in univariable models, a multivariable logistic regression model was performed and all factors remained statistically significant with the exception of gender. This reinforces that the presence of ADL and medical concerns and older age were associated with higher odds of mental health concerns (**Table 2**).

Mental Health as a Predictive Factor of Adverse Healthcare Outcomes

Three multivariable logistic regression models were performed for the risk of each adverse outcome (institutionalization, hospitalization, and death). Model 1 (M1) included the presence/absence of mental health concerns, model 2 (M2) included the severity of concerns and model 3 (M3) the ability of the caregiver network to manage risk. Gender, age, ADLs, and medical concerns were included as covariates. Results are presented in **Table 3**.

All three predictive factors (living alone, ADL concerns, and Medical concerns) of the three adverse healthcare outcomes were statistically significant. Patients with mental health concerns had greater odds of perceived risk of each adverse outcome (OR = 2.22, 95% CI 1.83–2.69 for risk of institutionalization; OR = 1.66, 95% CI 1.41–1.94 for risk of hospitalization; OR = 1.69, 95% CI 1.42–2.01 for risk of death). Additionally, as the severity of concern increased, the odds of perceived risk also increased (OR for each level of severity – mild, moderate and severe – varies between 1.11 and 5.41), compared to those without mental health concerns. Finally, the odds of perceived risk of each adverse outcome increased as the ability of the caregiver network to manage mental health concern decreased (from 'can manage,' to 'carer strain,' 'some gaps,' to 'cannot manage'): OR for each level of caregiver network varies between 1.07 and 16.9. Model 3 revealed a lower AIC for the risk of institutionalization, while model 2 showed a lower AIC for risk of hospitalization and death.

The results of ROC curve analysis are presented in **Table 4**. All models present an AUC greater than 0.80 (values varies between 0.810 and 0.838), suggesting good discriminatory capacity. Comparing the models for each outcome, only M1

TABLE 2 | Univariable and multivariable logistic regression models of mental health concerns.

	n	%	Unadjusted			Adjusted		
			OR	95% CI	*p*	OR	95% CI	*p*
Gender								
Male	608	32.8	1	–	0.001	1	–	0.293
Female	1008	38.1	1.26	1.11–1.43		1.08	0.93–1.25	
Age, years	–	–	1.08	1.07–1.09	<0.001	1.03	1.02–1.04	<0.001
Living alone								
No	1313	35.9	1	–				
Yes	272	37.1	0.95	0.81–1.12	0.566			
ADL concerns								
No	344	14.0	1	–	<0.001	1	–	<0.001
Yes	1272	62.3	10.1	8.76–11.7		7.15	6.08–8.41	
Medical concerns								
No	108	11.1	1	–	<0.001	1	–	<0.001
Yes	1508	42.8	6.02	4.88–7.44		1.96	1.55–2.49	

TABLE 3 | Multivariable logistic regression models of risk of adverse healthcare outcomes.

Model	Mental health	Risk of institutionalization			Risk of hospitalization			Risk of death		
		OR	95% CI	AIC	OR	95% CI	AIC	OR	95% CI	AIC
M1	Concerns									
	No	1	–	3197.7	1	–	4319.5	1	–	3761.3
	Yes	2.22	1.83–2.69		1.66	1.41–1.94		1.69	1.42–2.01	
M2	Severity									
	No	1	–	3127.5	1	–	4260.9	1	–	3673.6
	Mild	1.42	1.13–1.80		1.17	0.97–1.41		1.11	0.90–1.36	
	Moderate	2.81	2.21–3.57		2.28	1.83–2.84		2.09	1.66–2.62	
	Severe	5.30	3.82–7.36		3.85	2.66–5.57		5.41	3.79–7.72	
M3	Caregiver									
	No	1	–	2984.8	1	–	4262.8	1	–	3697.1
	Can manage	1.07	0.84–1.38		1.26	1.04–1.52		1.25	1.01–1.55	
	Carer strain	2.11	1.65–2.71		1.65	1.32–2.06		1.80	1.43–2.28	
	Some gaps	8.25	5.93–11.5		3.35	2.39–4.69		2.15	1.57–2.95	
	Cannot manage	16.9	9.48–30.2		6.44	3.41–12.2		10.3	5.66–18.7	

**Models adjusted for gender, age, ADL, and medical concerns.*

TABLE 4 | Discriminatory capacity of all three model to predict risk of adverse healthcare outcomes (AUC and standard error).

Model	Risk of institutionalization		Risk of hospitalization		Risk of death	
	AUC (SE)	*p**	AUC (SE)	*p**	AUC (SE)	*p**
M1	0.810 (0.007)	0.116	0.816 (0.006)	0.234	0.819 (0.007)	0.080
M2	0.824 (0.007)	0.005'	0.823 (0.006)	0.405'	0.828 (0.007)	0.050'
M3	0.838 (0.007)	0.084"	0.821 (0.006)	0.999"	0.826 (0.007)	0.697"

**p: comparing M1 and M2; p': comparing M1 and M3; p": comparing M2 and M3.*

was statistically different from the M3 considering perceived risk of institutionalization as outcome (AUC = 0.810 for M1 and AUC = 0.838 for M3, $p = 0.005$).

DISCUSSION

This study presents the prevalence of cases of mental health concerns (composite neurocognitive and mood disorders) in the selected study population, their severity, and the perceived ability of caregiver networks to manage and the perceived risk of adverse healthcare outcomes in a large sample of community-dwelling older adults in Portugal, scored by community healthcare professional using a new short, global risk assessment instrument, akin to a brief targeted geriatric assessment, called the RISC. The results show that 35.9% of older patients presenting to PC in northern Portugal are judged by their healthcare professional to have mental health concerns. The severity of these mental health concerns was generally mild (52.4%) although 34.6% were moderate and 13% severe. It is possible that those with mild mental health concerns do not fulfill the criteria to be diagnosed with mental health disorders but instead represent patients with subclinical mental health problems that nevertheless contribute to morbidity and mortality particularly in older people (Steffens et al., 2000; Xavier et al., 2013). The percentage of people aged 65 or more years with mental health problems, identified by the GPs in this study, is consistent with existing figures; the lifelong prevalence for mental health diseases in PC patients is estimated to be 42.7%, and the one year prevalence for the general Portuguese population is 22.6% (DGS, 2013).

Mental health concerns were higher in women, older people and people with physical and functional problems as expected but when the model was adjusted, gender was no longer significant suggesting that older age, disease and functional impairment are more relevant than gender itself.

In this study patients with mental health problems had high levels of comorbidity with 78% scored for physical and medical concerns using the RISC. ADL were also associated with mental health problems with 45.4% of the patients having functional impairment. This was found to increase perceived risk, as judged by healthcare professionals, of all three adverse healthcare outcomes of interest in this study: institutionalization, hospitalization, and death.

We found that the best predictors of mental health problems were older age, impairment in ADL and medical problems, stressing the relevance of functionality and also comorbidity in old age corroborating other studies (Paul et al., 2006; Lee and Lee, 2011; Veerbeek et al., 2014). Loss of independence in performing ADL is a major concern for older people impacting

upon self-perceived quality of life (Fernandez-Ballesteros et al., 2010). The relevance of caregiver networks to patients with mental health problems is established in the literature (Carretero et al., 2009) supporting other studies that suggest that competent caregiving can prevent risk of adverse outcomes (Giles et al., 2004). This study shows that almost half (48.5%) of caregiver networks were perceived by healthcare professionals in PC to be able to manage mental health concerns; however, a further 32.9% were deemed under strain and 5% unable to manage. The strain or burden placed on caregivers significantly increased the probability of perceived adverse outcomes, particularly for risk of institutionalization.

By comparing models we verified that the risk of institutionalization was increased when the caregiver network was deemed unable to cope. This again corroborates several studies stressing the importance of caregiver burden and its clear deleterious effects on older people including quality of life and increasing the cost of health and social care provision (Schulz and Martire, 2004).

This study has a number of limitations. The design was not able to examine point prevalence, but only the frequency or prevalence of cases in the selected study population. Thus, the sample is not probabilistic given that it was dependent on the willingness of the existing PC teams in the region to participate, introducing possible selection bias. This bias, however, does not affect the population selected, as most patients do not choose a GP but are assigned to one who is available. Further, this population-based study covers the whole northern region of Portugal increasing the external validity of the results. This cross-sectional study does not allow us to draw conclusions on a causal relationship between variables. Mental health, physical health and function are highly related such that mental disorders can be precursors of other chronic disease as well as the consequence of them (WHO and the Calouste Gulbenkian Foundation, 2014). The interaction between these conditions must be considered in screening and treatment strategies. Finally, this study presents the results of perceived rather than the actual risk of adverse outcomes, as scored by the RISC. Given the paucity of valid and reliable risk-prediction instruments available for use in the community (O'Caoimh et al., 2015a), the RISC seems a reasonable choice. Similar to the initial validation study in Ireland (O'Caoimh et al., 2012, 2015c) a prospective study is now underway in Portugal to determine whether the health care professionals predictions, as scored by the RISC, were able to accurately predict each of the three adverse outcomes of interest (institutionalization, hospitalization, and death) in Portugal. One-year outcomes are expected soon and further studies will investigate the predictive validity of the RISC against other risk-prediction instruments. The RISC is also being investigated in other populations and countries including Spain and Australia.

CONCLUSION

Awareness of the importance of screening and assessing mental health concerns in PC is increasing. The RISC is a short, subjective, global risk-prediction instrument that can be used to train healthcare professionals (GPs and nurses) to screen and triage older people at risk of adverse outcomes including those with mental health problems. This instrument, unlike many others, includes an assessment of the patients' caregiver networks in its risk assessment algorithm (O'Caoimh et al., 2015a). Scoring the RISC is quick, suggesting that it can easily be incorporated into routine clinical practice. This study reaffirms the high prevalence of mental health disorders in PC, especially those with mild or subclinical syndromes, and highlights important factors such as age, and the presence of physical comorbidities and functional impairment, and the outcomes that they are perceived to predict. Given the current demand for services and the prevailing shortage of resources, the need to triage patients will continue. Early identification of mental health concerns in older patients in PC should allow healthcare professionals initiate prompt, appropriate and directed treatment. Further research is now required to confirm these findings.

AUTHOR CONTRIBUTIONS

CP and LT developed the study aim and design. LT undertook the analyses. MA, SA, and MD conducted the fieldwork and contribute to the discussion. ROC and WM developed the measurement instrument and trained the researchers. CP coordinated writing of the paper. All authors contributed to the final version.

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Needs in Nursing Homes and Their Relation with Cognitive and Functional Decline, Behavioral and Psychological Symptoms

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Unmet needs are becoming acknowledged as better predictors of the worst prognostic outcomes than common measures of functional or cognitive decline. Their accurate assessment is a pivotal component of effective care delivery, particularly in institutionalized care where little is known about the needs of its residents, many of whom suffer from dementia and show complex needs. The aims of this study were to describe the needs of an institutionalized sample and to analyze its relationship with demographic and clinical characteristics. A cross-sectional study was conducted with a sample from three nursing homes. All residents were assessed with a comprehensive protocol that included Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS-15), Neuropsychiatric Inventory (NPI) and Adults and Older Adults Functional Inventory (IAFAI). To identify needs, the Camberwell Assessment of Need for the Elderly (CANE) was used. The final sample included 175 residents with a mean age of 81 standard deviation (SD = 10) years. From these, 58.7% presented cognitive deficit (MMSE) and 45.2% depressive symptoms (GDS). Statistically significant negative correlations were found between MMSE score and met (r_s = −0.425), unmet (r_s = −0.369) and global needs (r_s = −0.565). Data also showed significant correlations between depressive symptoms and unmet (r_s = 0.683) and global needs (r_s = 0.407), and between behavioral and psychological symptoms (BPSD) and unmet (r_s = 0.181) and global needs (r_s = 0.254). Finally, significant correlations between functional impairment and met (r_s = 0.642), unmet (r_s = 0.505) and global needs (r_s = 0.796) were also found. These results suggest that in this sample, more unmet needs are associated with the worst outcomes measured. This is consistent with previous findings and seems to demonstrate that the needs of those institutionalized elderly remain under-diagnosed and untreated.

Keywords: needs assessment, CANE, elderly, nursing home, dementia, depression, behavioral and psychological symptoms, functional dependency

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INTRODUCTION

With an aged population and the resultant increase of chronic diseases, including dementia, in the near future, the evaluation of the emergent needs of this population has become crucial (Cadieux et al., 2013). In fact, people are not only living longer, but also presenting important age-related diseases which are often chronic and associated with daily functional and mental limitations (Fahy and Livingston, 2001), which can eventually lead to their institutionalization (van der Ploeg et al., 2013). Therefore, institutionalization rates increase when elderly dependency levels and needs become too complex or costly to be met at home (Hancock et al., 2006; Orrell et al., 2007) or by the available community services. As a result, people living in long-term care settings often present dementia and other concomitant comorbid diseases that will not only increase their morbidity and mortality, but also result in multiple and complex needs in these care settings (Martin et al., 2002; Hancock et al., 2006; Orrell et al., 2007; Cadieux et al., 2013).

In this context, higher demands are imposed on nursing homes and other long term care facilities (Alzheimer's Association, 2014) as their residents are becoming older, frailer and more dependent (Stern et al., 1993; Martin et al., 2002) due to their physical and cognitive impairments (van der Ploeg et al., 2013). The way their complex needs are met is relatively unknown (Hancock et al., 2006), particularly if one considers older people with dementia (Lee et al., 2002) that often have their needs unmet (Cohen-Mansfield and Mintzer, 2005; Orrell et al., 2008), despite the importance of planning their care. In fact, there is scarce evidence on how far these institutions can identify and address the needs of their residents. However, it is well known that some of those needs may be neglected for a number of reasons, including their major complexity, the progressive inability of patients to express themselves (Mozley et al., 1999), or even due to resignation and hopelessness, leaving them as unmet needs (Holmquist et al., 2003; Hancock et al., 2006).

An unmet need is described as a problem for which an individual is not receiving an appropriate assessment or intervention that could potentially meet the need (Iliffe et al., 2004; Orrell and Hancock, 2004). Needs, particularly when unmet, are found to be important clinical and research targets. They lead to a decrease in quality of life (Slade et al., 2005; Hoe et al., 2006), higher anxiety, depression and challenging behaviors (Hancock et al., 2006), as well as predicting premature institutionalization and mortality (Gaugler et al., 2005). Once patients are in long-term care settings, unmet needs have been found to be associated with increased distress (Hoe et al., 2006; Orrell et al., 2008) and dissatisfaction with services. Research has also demonstrated that some characteristics, such as dementia diagnosis and severity, depression, anxiety, behavioral and psychological symptoms (BPSD), somatic disorders and dependency, are associated with greater unmet needs (Field et al., 2005; Hancock et al., 2006; Miranda-Castillo et al., 2010a,b).

In this context, unmet needs can be acknowledged as better predictors of the worst prognostic outcomes than the usual measures of functional or cognitive decline (Gaugler et al., 2005). These needs are also amenable to interventions that can improve health status, survival and function if followed up with active management (Stuck et al., 1993, 2004; Iliffe et al., 2004), as well as improving compliance with treatment, and quality of life (Miranda-Castillo et al., 2013). Their accurate assessment is becoming a pivotal component of effective care delivery (Challis et al., 2004) and their management a fundamental part of good health care (Ashaye et al., 2003). In order to assess and measure needs, some tools can be used for a comprehensive assessment and identification of common, important and treatable unmet needs (Iliffe et al., 2004). Once identified, the mapping of needs can be used to achieve individualized, person-centered, good-quality and effective care.

Taking this into account, the aims of the present study were to identify and describe the needs presented by an institutionalized sample and to investigate the impact of those needs on health and global functioning by analyzing their relation with other demographic and clinical characteristics.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional multi-center study was conducted in three nursing homes in northern Portugal, between September 2012 and April 2013. A list of residents was obtained for each nursing home that agreed to participate, and all residents were considered eligible. Inclusion criteria were being a permanent resident and being able to give informed consent or assent, depending on the level of cognitive abilities. Terminally ill residents, those with delirium, who were unresponsive or unwilling to complete the assessment were excluded. For each participant a staff member was also interviewed. The participating staff member had to know the resident's needs in order to be included.

Data Collection and Assessments

A structured interview to collect general information on socio-demographic status, medical history and pharmacological treatment was carried out. Regarding medication, drugs were coded both as continuous and dichotomous variables (present/absent) for major categories. Anatomical Therapeutic Chemical (ATC) classification (World Health Organization, 2013) was used to indicate the anatomical main group of each drug. Comorbidities were also coded following the individual body systems of the Cumulative Illness Rating Scale for Geriatrics (CIRS-G; Miller et al., 1992).

Needs were assessed with the Camberwell Assessment of Need for the Elderly (CANE; Reynolds et al., 2000; Orrell and Hancock, 2004; range: 0–24), a comprehensive assessment tool for older people that covers 24 areas of social, physical, psychological, and environmental needs. It includes the views of the elderly, their carers and health professionals, allowing a comparison of perspectives. Overall, ratings were made by the evaluator based on the gathered information regarding the different perspectives, and each area was rated as: no need (absence of problem), met need (problem area

receiving appropriate assessment or intervention), or unmet need (problem area requiring further assessment, neither receiving appropriate intervention nor receiving intervention at all). CANE presents very good validity and reliability and these properties have already been studied for the Portuguese population (Fernandes et al., 2009). Once the ratings from the evaluator were obtained for all residents (n = 175), only these are reported.

Study protocol also included the Mini-Mental State Examination (MMSE; Folstein et al., 1975) used as a brief measure of cognitive function (range: 0–30), Geriatric Depression Scale 15 items (GDS-15; Yesavage et al., 1983) a brief screening scale of depressive symptoms (range: 0–15), Adults and Older Adults Functional Assessment Inventory (IAFAI; Sousa et al., 2014) a Portuguese measure that assesses functional incapacity (range: 0–100%), and the European Portuguese version of Neuropsychiatric Inventory (NPI; Cummings et al., 1994) used to assess BPSD (range: 0–144). The validity and reliability of the Portuguese versions of MMSE, GDS and NPI have already been established (Guerreiro et al., 1994; Ferreira et al., 2015; Simões et al., 2015, respectively).

All protocol measures were administered in accordance with written instructions and manuals. The interviews took place in a quiet room, and separate interviews were conducted with staff members to assess the residents' current met and unmet needs and BPSD.

For analysis proposes the cognitive decline and dementia severity was staged according MMSE ranges as: absent (MMSE of 30), questionable (26–29), mild (21–25), moderate (scores between 11 and 20) and severe dementia (MMSE score $\leq$10; Perneczky et al., 2006). Likewise, considering previous studies, a score $\geq$4 on NPI was considered indicative of clinically relevant BPSD (Lyketsos et al., 2002), and a GDS-15 score $>$5 was used to signal significant depressive symptoms (Simões et al., 2015).

Ethical Considerations

The study protocol was approved by the scientific committee of the PhD Program in Clinical and Health Services Research/University of Porto. The project was approved by the three nursing home review boards (Nursing Home of Segurança Social of Porto, Instituição Particular de Solidariedade Social of Porto and Instituição Particular de Solidariedade Social of Matosinhos).

All the participants gave their written informed consent before the beginning of the assessment.

Data Analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 for Windows. Descriptive statistics regarding demographics were calculated. Categorical variables were described through absolute frequencies, and continuous variables through mean and standard deviation (SD), median, minimum and maximum (range). Hypotheses on the distribution of continuous variables without normal distribution were tested by the non-parametric tests Mann-Whitney and Kruskal-Wallis, and to assess the strength and direction of associations between continuous variables Spearman's correlation coefficients were calculated. Where needs were not normally distributed, non-parametric tests were chosen. All significance tests were performed at a two-tailed alpha level of 0.05.

RESULTS

Sample Characteristics

The sample included 248 residents out from the eligible ones. From these, 73 residents (29.4%) were not included due to incapacity related to advanced dementia, acute illness or aphasia (n = 62), refusal (n = 1), hospitalization (n = 5) or death (n = 5) throughout the study time. The non-participants had lived on average in the homes for longer (11 vs. 7 years, p = 0.005) and were more severely impaired than the residents who participated. There were no significant differences regarding the average age of both groups (82 vs. 81 years, p = 0.361).

The mean age of the final sample (n = 175) was 81 (SD = 10, range: 47–103) years. Participants were mostly females (90%), widowed (51%), with a low education level (86.1% ranging from 0 to 4 years) and low socioeconomic status (77.6% low and very low status according to Graffar classification). The average length of institutionalization was 7 (SD = 11, range: 0–61) years. The main demographic and clinical characteristics of the sample are presented in **Table 1**.

TABLE 1 | Demographic and clinical characteristics of residents.

Patients' characteristics	
Age, years (SD)	81 (10)
Gender, n (%)	
Male	18 (10)
Female	157 (90)
Marital status, n (%)	
Single	55 (31)
Married	12 (7)
Separated/Divorced	19 (11)
Widowed	89 (51)
Socio-economic classification (Graffar)[1], n (%)	
Very high	1 (0.6)
High	10 (5.9)
Median	27 (15.9)
Low	68 (40.0)
Very low	64 (37.6)
Education[2], years (SD)	3 (4)
Duration of institutionalization, years (SD)	7 (11)
Number of medications[3], mean (SD)	7 (3)
Number of comorbidities[3], mean (SD)	9 (4)
Cognitive impairment (MMSE)[3], mean (SD)	22 (6)
Depression (GDS)[4], mean (SD)	5 (4)
Functional status (IAFAI)[5], mean (SD)	43.5 (23.5)
Behavioral and psychological symptoms (NPI)[4], mean (SD)	6 (12)

MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; IAFAI, Adults and Older Adults Functional Assessment Inventory; NPI, Neuropsychiatric Inventory. [1]*Variable with 5 missing cases;* [2]*Variable with 8 missing cases;* [3]*Variables with 3 missing cases;* [4]*Variables with 9 missing cases;* [5]*Variable with 24 missing cases.*

Most residents presented health problems with an average of 9 (SD = 4, range: 2–22) co-morbid medical conditions, and consumed medications for various purposes with a mean of 7 (SD = 3, range: 0–15). Of this sample, 86.0% consumed medication for the cardiovascular system, 79.1% for the nervous system and 68.6% for blood and blood-forming organs (**Table 2**).

Met and Unmet Needs

Twelve residents (6.9%) were unable to understand the CANE questions. For them, only the health professional and evaluator perspectives were obtained. Additional comparisons were conducted among those who could and could not complete CANE. Residents who were unable to complete the questionnaire were significantly more cognitively impaired (MMSE mean 22 vs. 18, $p = 0.022$). There were no significant differences regarding age ($p = 0.159$), average length of institutionalization ($p = 0.094$), depressive symptomatology ($p = 0.065$) or behavior ($p = 0.635$).

Overall 2162 needs were identified, 1523 (70.4%) were met and 639 (29.6%) unmet. The average number of needs identified was 12 (SD = 4, range: 3–18), 9 (SD = 3, range: 1–15) being met and 4 (SD = 2, range: 0–11) unmet. One hundred and seventy (97.1%) out of 175 residents presented one or more unmet needs, and the number of unmet needs did not significantly differ across the three nursing homes (mean 4 vs. 3 vs. 4, $p = 0.514$). The frequencies of CANE identified needs (met and unmet) are presented in **Table 3**. All residents were receiving adequate assistance for accommodation (100%), and almost all required and were receiving suitable assistance with household skills (96.6%), food (93.1%), physical health (93.1%), drugs (77.7%) and money (76.6%). The most frequent unmet needs were daytime activities (73.1%), followed by eyesight and hearing (67.4%), psychological distress (52.0%), company (40.6%) and memory (37.1%). Unmet needs presented a significant positive correlation with the age of residents ($r_s = 0.236$, $p = 0.002$), and a negative one with the time of institutionalization ($r_s = -0.248$, $p = 0.001$), but none with gender ($p = 0.768$).

TABLE 2 | Frequencies of consumed drugs according to ATC classification.

ATC categories (*n* = 172)	*n* (%)
Alimentary tract and metabolism	101 (58.7)
Blood and blood forming organs	118 (68.6)
Cardiovascular system	148 (86.0)
Dermatologicals	0 (0)
Genito urinary system and sex hormones	14 (8.1)
Systemic hormonal preparations, excl. sex hormones and insulins	9 (5.2)
Antiinfectives for systemic use	3 (1.7)
Antineoplastic and immunomodulating agents	0 (0)
Musculo-skeletal system	38 (22.1)
Nervous system	136 (79.1)
Antiparasitic products, insecticides and repellents	0 (0)
Respiratory system	20 (11.6)
Sensory organs	10 (5.8)
Various	1 (0.6)

TABLE 3 | Frequency of CANE needs.

	Needs identified *n* (%)		
Need/Domains	**No need**	**Met need**	**Unmet need**
Accommodation	175 (100.0)	–	–
Household skills	6 (3.4)	169 (96.6)	–
Food	12 (6.9)	163 (93.1)	–
Self-care	48 (27.4)	127 (72.6)	–
Caring for other	175 (100.0)	–	–
Daytime activities	20 (11.4)	27 (15.4)	128 (73.1)
Memory	85 (48.6)	25 (14.3)	65 (37.1)
Eyesight/Hearing	31 (17.7)	26 (14.9)	118 (67.4)
Mobility	66 (37.7)	85 (48.6)	24 (13.7)
Continence	113 (64.6)	61 (34.9)	1 (0.6)
Physical health	–	163 (93.1)	12 (6.9)
Drugs	34 (19.4)	136 (77.7)	5 (2.9)
Psychotic symptoms	114 (65.1)	40 (22.9)	21 (12.0)
Psychological distress	34 (19.4)	50 (28.6)	91 (52.0)
Information	80 (45.7)	88 (50.3)	7 (4.0)
Safety (deliberate self-harm)	152 (86.9)	11 (6.3)	12 (6.9)
Safety (accidental self-harm)	66 (37.7)	102 (58.3)	7 (4.0)
Abuse/neglect	156 (89.1)	17 (9.7)	2 (1.1)
Behavior	99 (56.6)	67 (38.3)	9 (5.1)
Alcohol	168 (96.0)	4 (2.3)	3 (1.7)
Company	93 (53.1)	11 (6.3)	71 (40.6)
Intimate relationships	115 (65.7)	2 (1.1)	58 (33.1)
Money	37 (21.1)	134 (76.6)	4 (2.3)
Benefits	159 (90.9)	15 (8.6)	1 (0.6)

Needs and Cognitive Decline

A total of 172 residents (98.3%) completed the MMSE. The sample scored an average of 22 (SD = 6, range: 5–30) on MMSE, and 101 (58.7%) participants scored for cognitive decline. For those with cognitive decline, the mean number of unmet needs identified was 4 (SD = 2, range: 1–11) compared to a mean of 3 (SD = 2, range: 0–8) for those without ($p < 0.001$; **Figure 1**). Cognitively impaired participants had unmet needs in the areas of daytime activities ($p < 0.001$), memory ($p < 0.001$) and psychotic symptoms ($p = 0.005$), that differed significantly from those without decline (**Table 4**). Data were also analyzed in order to compare unmet needs by severity stages of dementia as defined by Perneczky et al. (2006). Accordingly, the sample was divided into five groups: no decline ($n = 6$), questionable ($n = 55$), mild ($n = 45$), moderate ($n = 61$) and severe ($n = 5$) dementia. **Table 5** presents the frequency of unmet needs identified across the stages of the disease. Early stages had more unmet needs in daytime activities (73.3%), eyesight/hearing (71.1%) and psychological distress (55.6%) domains, whereas residents in the moderate stage presented more needs related to memory (63.9%), psychotic symptoms (23.0%) and behavior (6.6%), compared to the former stage. Among the severe stage, daytime activities (100%), memory (100%) and eyesight/hearing (80.0%) were the most frequently rated unmet needs. A significant negative correlation was found between MMSE score (greater impairment) and the number of met ($r_s = -0.425$, $p < 0.001$), unmet ($r_s = -0.369$, $p < 0.001$) and global needs ($r_s = -0.565$, $p < 0.001$).

Needs and Depressive Symptoms

Of the 175 participants, 166 (94.9%) completed the GDS-15, and their average score was 5 (SD = 6, range: 0–14). The study

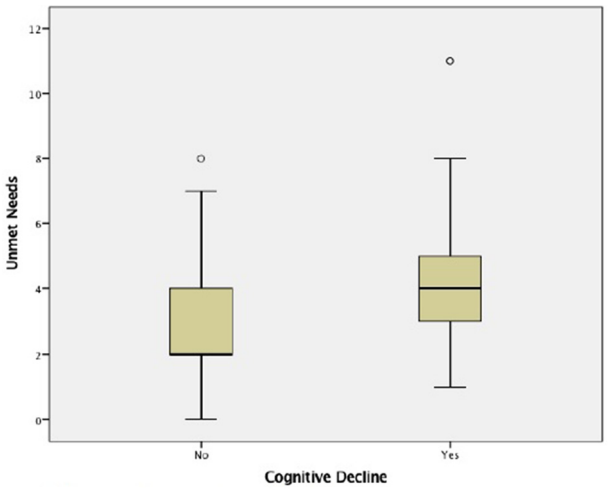

FIGURE 1 | Unmet needs considering cognitive decline.

TABLE 4 | Unmet needs considering cognitive decline.

	Needs identified *n* (%) Cognitive decline		
Need/Domains	**Without (*n* = 71)**	**With (*n* = 101)**	***p*-value[1]**
Accommodation	–	–	–
Household skills	–	–	–
Food	–	–	–
Self-care	–	–	–
Caring for other	–	–	–
Daytime activities	40 (56.3)	85 (84.2)	<0.001
Memory	5 (7.0)	57 (56.4)	<0.001
Eyesight/Hearing	48 (67.6)	67 (66.3)	0.161
Mobility	6 (8.5)	17 (16.8)	0.267
Continence	0 (0)	1 (1.0)	<0.001
Physical health	4 (5.6)	7 (6.9)	0.766
Drugs	2 (2.8)	3 (3.0)	<0.001
Psychotic symptoms	3 (4.2)	17 (16.8)	0.005
Psychological distress	37 (52.1)	51 (50.5)	0.061
Information	0 (0)	4 (4.0)	<0.001
Safety (deliberate self-harm)	6 (8.5)	5 (5.0)	0.777
Safety (accidental self-harm)	2 (2.8)	5 (5.0)	0.001
Abuse/neglect	1 (1.4)	1 (1.0)	0.901
Behavior	1 (1.4)	6 (5.9)	0.254
Alcohol	2 (2.8)	1 (1.0)	0.596
Company	26 (36.6)	43 (42.6)	0.393
Intimate relationships	22 (31.0)	35 (34.7)	0.874
Money	0 (0)	4 (4.0)	<0.001
Benefits	1 (1.4)	0 (0)	0.259

[1]*Chi-Square test.*

sample was also divided on the basis of GDS score. From the whole sample, 75 residents (45.2%) scored for depression (GDS scores ranged from 5 to 15). Unmet needs were more common in residents who scored for depression. Elderly with depression presented a mean of 5 unmet needs (SD = 2, range: 2–11) compared to those without who had a mean of 3 (SD = 2, range: 0–8; $p < 0.001$; **Figure 2**). Considering the presence of depressive symptoms, psychological distress ($p < 0.001$), daytime activities ($p = 0.022$), company ($p < 0.001$) and intimate relationships ($p < 0.001$) domains differed significantly between the groups (**Table 6**). Data also showed significant correlations between the presence of depressive symptoms assessed by GDS and unmet ($r_s = 0.683$, $p < 0.001$) and global needs ($r_s = 0.407$, $p < 0.001$), while no significant association were found with met needs ($r_s = 0.011$, $p = 0.889$).

Needs and Behavioral and Psychological Symptoms

Concerning BPSD, at screening 50.6% of the sample presented at least one symptom, and 56 (33.7%) scored above the NPI cut-off for clinical significance. The average NPI score was 6 (SD = 12, range: 0–76). The most common BPSD across the sample were sleep and nighttime behavior change (54%), delusions (22%), dysphoria/depression (19%), irritability/lability (17%) and agitation/aggression (15%), while the least prevalent were elation/euphoria (3%), aberrant motor behavior (4%) and disinhibition (5%). These results have been described in detail elsewhere (Ferreira et al., 2015). Those with more BPSD had significantly more global needs (mean 14 vs. 13, $p = 0.008$; **Figure 3**), particularly in the areas of psychotic symptoms ($p < 0.001$), behavior ($p < 0.001$) and mobility ($p = 0.006$; **Table 7**). Significant correlations between the presence of BPSD and unmet and global needs ($r_s = 0.181$, $p = 0.020$; $r_s = 0.254$, $p = 0.001$, respectively) were found, but not with those being met ($r_s = 0.152$, $p = 0.051$).

Needs and Functional Dependency

Of the 175 participants, 151 (86.3%) completed the IAFAI, and their average score was 43.5% (SD = 23.5%, range: 0–93.6%). The functional dependency was correlated with greater unmet needs. Significant correlations between functional dependency and met ($r_s = 0.642$, $p < 0.001$), unmet ($r_s = 0.505$, $p < 0.001$) and global needs ($r_s = 0.796$, $p < 0.001$) were found.

DISCUSSION

The main aim of the present study was to describe the met and unmet needs of residents in nursing homes. To our knowledge this is the first study systematically conducted with this purpose in the northern Portugal.

Needs assessment has become a central issue following the growing recognition that it could lead to more appropriate and effective provision of care, services and resource usage (Worden et al., 2006). Overall, and in line with previous studies (Holmquist et al., 2003; Hancock et al., 2006), unmet needs were prevalent across these three nursing homes, and clustered in particular domains, namely the psychosocial, such as daytime activities, company and psychological distress (Martin et al., 2002; Hancock et al., 2006; Cohen-Mansfield et al., 2015). Needs rated in the areas of daytime activities and company, are a trend in these long-term care settings that has been encountered by previous researchers (Mozley et al., 2000; Hancock et al., 2006; Orrell et al., 2008; Popham and Orrell, 2012) and systematic reviews (e.g., Cadieux et al., 2013). Sensory needs and memory were also found to be among the

TABLE 5 | Unmet needs across severity stages of dementia.

Need/Domains	Needs identified *n* (%)				
	No (*n* = 6)	Questionable (*n* = 55)	Mild (*n* = 45)	Moderate (*n* = 61)	Severe (*n* = 5)
Accommodation	–	–	–	–	–
Household skills	–	–	–	–	–
Food	–	–	–	–	–
Self-care	–	–	–	–	–
Caring for other	–	–	–	–	–
Daytime activities	3 (50.0)	31 (56.4)	33 (73.3)	53 (86.9)	5 (100.0)
Memory	0 (0)	1 (1.8)	17 (37.8)	39 (63.9)	5 (100.0)
Eyesight/Hearing	1 (16.7)	39 (70.9)	32 (71.1)	39 (63.9)	4 (80.0)
Mobility	1 (16.7)	3 (5.5)	5 (11.1)	11 (18)	3 (60.0)
Continence	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)
Physical health	0 (0)	1 (1.8)	5 (11.1)	5 (8.2)	0 (0)
Drugs	0 (0)	2 (3.6)	1 (2.2)	2 (3.3)	0 (0)
Psychotic symptoms	0 (0)	4 (7.3)	1 (2.2)	14 (23)	1 (20.0)
Psychological distress	3 (50)	27 (49.1)	25 (55.6)	31 (50.8)	2 (40.0)
Information	0 (0)	0 (0)	0 (0)	3 (4.9)	1 (20.0)
Safety (deliberate self-harm)	1 (16.7)	3 (5.5)	5 (11.1)	2 (3.3)	0 (0)
Safety (accidental self-harm)	0 (0)	3 (5.5)	1 (2.2)	3 (4.9)	0 (0)
Abuse/neglect	1 (16.7)	0 (0)	0 (0)	1 (1.6)	0 (0)
Behavior	0 (0)	1 (1.8)	1 (2.2)	4 (6.6)	1 (20.0)
Alcohol	0 (0)	3 (5.5)	0 (0)	0 (0)	0 (0)
Company	1 (16.7)	21 (38.2)	15 (33.3)	31 (50.8)	1 (20.0)
Intimate relationships	2 (33.3)	17 (30.9)	13 (28.9)	24 (39.3)	1 (20.0)
Money	0 (0)	0 (0)	2 (4.4)	2 (3.3)	0 (0)
Benefits	0 (0)	1 (1.8)	0 (0)	0 (0)	0 (0)

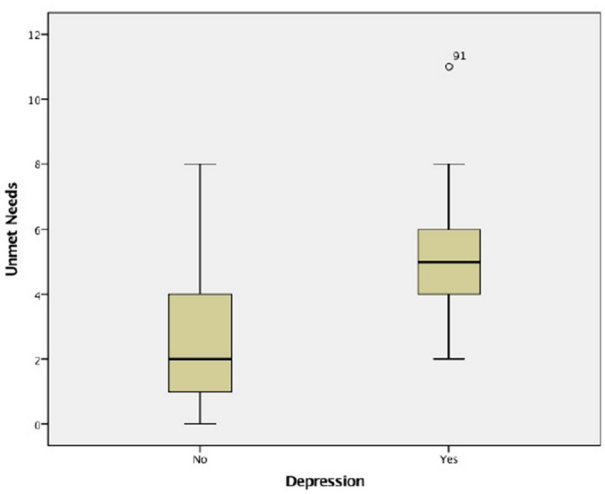

FIGURE 2 | Unmet needs considering depressive symptoms.

most prevalent in this sample, in accordance with findings by Hancock et al. (2006). Memory was also the highest ranked unmet domain (80.2%) found by Iliffe et al. (2004) in their sample of elderly residents. The present results are also in accordance with previous Portuguese studies conducted in psychiatry and mental health services in northern Portugal (Fernandes et al., 2009; Passos et al., 2012) regarding the most common unmet domains, except for eyesight/hearing found in the present study, and for social benefits and continence areas found by Passos et al. (2012).

TABLE 6 | Unmet needs considering depressive symptoms.

Need/Domains	Needs identified *n* (%)		*p*-value[1]
	No depression (*n* = 91)	Depression (*n* = 75)	
Accommodation	–	–	–
Household skills	–	–	–
Food	–	–	–
Self-care	–	–	–
Caring for other	–	–	–
Daytime activities	58 (63.7)	61 (81.3)	0.022
Memory	32 (35.2)	27 (36.0)	0.72
Eyesight/Hearing	55 (60.4)	55 (73.3)	0.172
Mobility	11 (12.1)	12 (16.0)	0.078
Continence	0 (0)	1 (1.3)	0.326
Physical health	3 (3.3)	7 (9.3)	0.188
Drugs	1 (1.1)	4 (5.3)	0.166
Psychotic symptoms	6 (6.6)	14 (18.7)	0.013
Psychological distress	19 (20.9)	68 (90.7)	<0.001
Information	2 (2.2)	2 (2.7)	0.953
Safety (deliberate self-harm)	1 (1.1)	10 (13.3)	0.002
Safety (accidental self-harm)	2 (2.2)	5 (6.7)	0.322
Abuse/neglect	1 (1.1)	1 (1.3)	0.276
Behavior	4 (4.4)	3 (4.0)	>0.999
Alcohol	2 (2.2)	1 (1.3)	>0.999
Company	14 (15.4)	53 (70.7)	<0.001
Intimate relationships	17 (18.7)	39 (52.0)	<0.001
Money	2 (2.2)	2 (2.7)	0.842
Benefits	0 (0)	1 (1.3)	0.211

[1]*Chi-Square test.*

A negative relationship between lengths of residency and the number of unmet needs was also found, which indicates that the longer the resident had lived in the home, the less their unmet

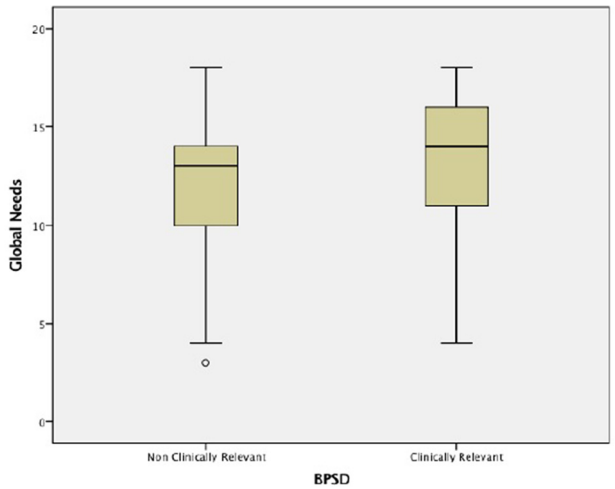

FIGURE 3 | Global needs considering behavioral and psychological symptoms.

TABLE 7 | Unmet needs considering behavioral and psychological symptoms.

Need/Domains	Needs identified *n* (%)		*p*-value[1]
	Non clinically relev. (*n* = 110)	Clinically relev. (*n* = 56)	
Accommodation	–	–	–
Household skills	–	–	–
Food	–	–	–
Self-care	–	–	–
Caring for other	–	–	–
Daytime activities	75 (68.2)	46 (82.1)	0.151
Memory	37 (33.6)	26 (46.4)	0.15
Eyesight/Hearing	74 (67.3)	38 (67.9)	0.939
Mobility	15 (13.6)	8 (14.3)	0.006
Continence	0 (0)	1 (1.8)	0.486
Physical health	10 (9.1)	2 (3.6)	0.227
Drugs	3 (2.7)	2 (3.6)	0.654
Psychotic symptoms	3 (2.7)	18 (32.1)	<0.001
Psychological distress	57 (51.8)	31 (55.4)	0.105
Information	4 (3.6)	3 (5.4)	0.237
Safety (deliberate self-harm)	7 (6.4)	5 (8.9)	0.596
Safety (accidental self-harm)	5 (4.5)	2 (3.6)	0.601
Abuse/neglect	2 (1.8)	0 (0)	0.583
Behavior	1 (0.9)	8 (14.3)	<0.001
Alcohol	1 (0.9)	2 (3.6)	0.197
Company	43 (39.1)	25 (44.6)	0.265
Intimate relationships	38 (34.5)	18 (32.1)	0.566
Money	1 (0.9)	3 (5.4)	0.19
Benefits	1 (0.9)	0 (0)	>0.999

[1]*Chi-Square test.*

needs were rated. Environmental and physical health needs were generally met, as had already been found by others not only in long-term care (Martin et al., 2002; Hancock et al., 2006; Orrell et al., 2008) but also in other settings like primary care (e.g., Walters et al., 2000). Those needs of a more basic or instrumental nature, such as accommodation, self-care, or food preparation, seem consistently met, apart from any specific psychopathology or disability, suggesting that long-term care settings are effective in identifying and meeting them.

The number of unmet needs presented by this sample is greater than those reported by other studies conducted in long term care (Martin et al., 2002; van der Ploeg et al., 2013; Cohen-Mansfield et al., 2015) and in other settings such as the community (van der Roest et al., 2009; Miranda-Castillo et al., 2010a,b), primary care (Hoogendijk et al., 2014), sheltered accommodation (Field et al., 2005) or psychiatric day hospitals (Ashaye et al., 2003). However, they agree with the data found by Orrell et al. (2007) at baseline in both their experimental and control groups (4.77 and 4.12 unmet needs on average, respectively), by Hancock et al. (2006; 4.4 unmet needs on average per resident), or by Greaves et al. (2006; 4.46 unmet needs found in a sample of patients that were referred to a psychiatric liaison service). Differences between settings agree with the fact that in institutional care, residents present a higher prevalence of other concurrent problems, such as depression, behavior, physical dependency and social problems (Fahy and Livingston, 2001). On the other hand, differences within long term-care settings may reflect different inclusion and referral criteria, as well as variance in the applied study designs and methodologies.

As noted by Miranda-Castillo et al. (2013), these consistent findings from different studies and settings should be a matter of concern. In fact, there are specific areas or domains in which unmet needs are more likely to occur, namely the domains of psychological distress, company and daytime activities, which are consistently reported as unmet (de Boer et al., 2007; van der Roest et al., 2007, 2009; Orrell et al., 2008; Miranda-Castillo et al., 2010a,b; von Kutzleben et al., 2012; Hoogendijk et al., 2014; Mazurek et al., 2015), and yet they tend to remain unmet despite this. Bearing this in mind, these findings convey an important message concerning the importance of effective management of mood disorders in nursing care, along with the involvement of the elderly in their own care (Orrell et al., 2008). It is worth noting that even residents who scored for moderate or severe decline in MMSE also gave pertinent information on their needs, and those also converge mainly in psychosocial areas, which has already been confirmed by other researchers (e.g., Orrell et al., 2008; Popham and Orrell, 2012). In fact, most residents are able to understand what people say or to interact sociably (Rocha et al., 2013), suggesting that the encouragement of multi-dimensional activities and participation could help to address some of those residents' unmet needs.

The study also sought to determine whether the number of needs was related to other important variables. Overall, in this sample more unmet needs were associated with the worst outcomes measured. In line with other studies, the presence of unmet needs was associated with increased cognitive and functional decline (Martin et al., 2002), as well as with more depressive symptoms (Field et al., 2005; Hancock et al., 2006; Mazurek et al., 2015) and BPSD (Hancock et al., 2006; Miranda-Castillo et al., 2010a). Unmet needs were positively associated with the number of BPSD, and it is worth noting that these symptoms can predict cognitive and functional decline, higher unmet needs (Miranda-Castillo et al., 2010a,b),

are associated with the current and future disease progression (Wadsworth et al., 2012), as well as tending to boost premature institutionalization (Yaffe et al., 2002; Herrmann et al., 2006; Scarmeas et al., 2007). In this sample, a high proportion of residents 80.8% presented psychiatric morbidity, which also comprises depressive symptoms. The high level of depressive symptomatology found (45.2%) is consistent with other cross-sectional studies (e.g., Mozley et al., 2000). Depression has not only been described as the commonest psychiatric disorder of later life (Katz et al., 1989), which can exist in association with other significant medical conditions, but has also been shown to be more prevalent in nursing home residents. It is important to verify that depression in nursing homes is heterogeneously presented and some of its symptoms such as apathy, withdrawal or disengagement are also considered as nonspecific signs of deterioration (Katz et al., 1989).

It is noteworthy that except for the age of residents, unmet needs were positively correlated with modifiable or treatable characteristics such as the presence of depressive symptoms or behavioral problems. These are areas that have also been found amenable to interventions planned by mental health professionals (Orrell et al., 2007), rather than relying solely on pharmacological approaches (Fossey et al., 2006). Therefore, appropriate assessment and interventions focused on these factors could provide opportunities to decrease the frequency of unmet needs (Miranda-Castillo et al., 2010a; Cadieux et al., 2013).

The study has some potential limitations and caution should be exercised upon generalization of the present findings. Firstly, its cross-sectional design, with findings that may point toward some important relations but that cannot imply causality. Considering the inclusion and exclusion criteria that were fixed, it is possible that those elderly with more unmet needs were under-recruited due to their incapacity to respond to the evaluation. In this way, the present non-random sample may be less disabled than the actual institutionalized population, which may have led to an underestimation of the real number of needs. Since the residents' participation was voluntary, it may have induced a positive bias into the findings. Finally, despite the discrepancy of the gender ratio presented in this sample, it is in line with other studies conducted in comparable settings (e.g., Hancock et al., 2006).

Despite the referred limitations, the study also has strengths. Firstly, valid and reliable measures were used. Secondly, the participants were included from various stages of dementia decline. This continuum is thought to represent and capture the range of needs over time in the disease progression. Thirdly, the study included a relatively large sample of residents and a detailed and standardized tool to access needs was applied. Considering the prognostic value of unmet needs, their evaluation should become a standard part of clinical evaluation providing important information to professionals, elderly and caregivers. Finally, as already noted in other studies (Walters et al., 2000; Orrell et al., 2007) CANE was also used as a means for coaching care staff about the range of needs and potential interventions.

Most studies have assessed needs using a cross-sectional approach (e.g., Field et al., 2005; Hancock et al., 2006; van der Ploeg et al., 2013), thus the longitudinal role of unmet needs is less well defined. Considering that the elderly population has been steadily increasing, further studies should not only include more homogeneous care facilities and larger samples, but also should imply prospective longitudinal approaches and focus on the relationships between unmet needs and clinical variables.

In conclusion, the present study was a contribution to the characterization of needs in nursing homes, which should be promoted in order to improve strategies for future care with different and complementary perspectives integrated into collaborative and tailored elderly care plans.

AUTHOR CONTRIBUTIONS

LF defined and designed the study and supervised the data collection. ARF collected the data. LF and ARF drafted the article. CCD carried out the statistical analyses. All the authors contributed to the interpretation of the data, revision of the article, and approved the final manuscript.

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frontiers in Aging Neuroscience

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Direct costs of dementia in nursing homes

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Dementia represents an economical burden to societies nowadays. Total dementia expenses are calculated by the sum of direct and indirect costs. Through the stages of the diseases, as the patients may require institutionalization or a formal caregiver, the direct costs tend to increase. This study aims to analyze the direct costs of dementia in Portuguese nursing homes in 2012, compare the spending between seniors with and without dementia, and propose a predictive costs model. The expenses analysis was based on (1) the use of emergency rooms and doctor's appointments, either in public or private institutions; (2) days of hospitalization; (3) medication; (4) social services use; (5) the need for technical support; and (6) the utilization of rehabilitation services. The sample was composed of 72 people, half with dementia and half without. The average annual expense of a patient with dementia was €15,287 thousand, while the cost of a patient without dementia was about €12,289 thousand. The variables "ability to make yourself understood," "self-performance: getting dressed" and "thyroid disorders" were found to be statistically significant in predicting the expenses' increase. In nursing homes, in 2012, the costs per patient with dementia were 1, 2 times higher than per patient without dementia.

Keywords: dementia, direct costs, nursing homes, economics, cost of illness, Portugal

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Introduction

Dementia encompasses a number of diseases and conditions with specific characteristics, such as cognitive impairment, functional, and behavioral (Reitz et al., 2011), and is a major cause of disability in old age (World Health Organization and Alzheimer's Disease International, 2012).

In 2010, the number of people with dementia in the world was estimated at 35.6 million. It is expected that the number will reach 65.7 million in 2030 and 115.4 million in 2050 (Ferri et al., 2005; World Health Organization and Alzheimer's Disease International, 2012).

The economic impact of dementia in society is connected with the resources used to prevent, diagnose, treat, rehabilitate, and cope with the illness (Huang et al., 1988; O'Shea and O'Reilly, 2000).

The total cost of dementia is produced by finding the sum of two types of costs, direct and indirect (Jönsson, 2004; Castro et al., 2010).

Indirect costs represent lost resources. These relate to the loss or reduction of earnings by the patient and/or family members arising from the lost or reduced productivity associated with premature death or absenteeism from work due to dementia (Jönsson, 2004; Castro et al., 2010).

The direct costs represent the resources used (Wimo et al., 2007), which tend to increase with the progression of the disease, with institutionalization, or when there is a need for a caregiver.

The costs of these resources are evaluated directly from the market value of goods and services (Huang et al., 1988). Direct costs include all of the costs directly accountable, from the medical and non-medical sector, which include hospital stays, medical services, medical drugs, social services, rehabilitation services, and formal payments to family caregivers (Jönsson, 2004; Castro et al., 2010). Institutionalization converts indirect costs into direct ones (Castro et al., 2010).

In 2008, the EuroCoDe project, considering 7.23 million people with dementia, estimated that the total cost of dementia in the European Union 27 (EU27) was around €160 billion (€22,000 per patient per year). Out of this amount, 56% of the cases were attributed to informal care costs and the remaining 44% to direct costs (Wimo et al., 2011).

The direct costs of dementia care were estimated to be US$279 billion when looking at 34.4 million cases of dementia in 2009 (Wimo et al., 2010).

In Portugal, in 2005, there were estimated to be approximately 113,039 people with dementia representing a direct cost of US$952.9 million (Wimo et al., 2007). In 2009, out of 142,790 diagnosed cases of dementia, the direct costs increased to US$1296.5 million (Wimo et al., 2010).

This study aims to analyze the direct costs of dementia in Portuguese nursing homes in 2012, compare the spending between seniors with and without dementia, and propose a predictive costs model using the selected variables of the Resident Assessment Instrument-Resource Utilization Group (RAI-RUG) (Gray et al., 2008). The RAI-RUG is one of the Quality Control System tools of gerontology, and it is considered the most complex one of them all. This protocol is a document of the Unit for Research and Education on Adults and Elders (UNIFAI).

Methods

Subjects

Firstly, by convenience and through the technique of non-probability sample (Ritchie and Lewis, 2003), four non-profit organizations that fell within the requirements of the RAI-RUG were included. In these four institutions, all the subjects selected were in nursing homes with a clinical diagnosis and signs of dementia.

The selection of subjects with signs of dementia was made by the nursing staff and the technical director of the institutions.

The diagnosis of dementia is a complicated process, takes a long time and carries a high economic cost (Zhu and Sano, 2006). For this reason, a several number of subjects had several signs of dementia (memory loss, disorientation, confusion, personality changes, among others World Health Organization and Alzheimer's Disease International, 2012), understood by health workers (nurses and doctors) but did not have a diagnosis definitive. Whereas a number of subjects would be left out of the study for not having a clinical diagnosis written, and in the presence of consensus between the team of PISS, these users were incorporated into the study. These signs have been checked by the team over the daily routines of the subject and in conversation with the elements of direct relationship of the person, such as family.

An equal number of subjects without dementia were included through the random paired sampling technique (Datallo, 2010). The sample was composed of 72 people, half with dementia and half without. Socio-demographic information of the sample can be seen in **Table 1**. Clients who were admitted after the evaluation of RAI-RUG were not included.

An informed consent was not signed because we did not have access to personal information or identification. Authorization was requested to charge each institution for accessing the documents required for data collection.

Analyzing the results it turns out that people included in the group without dementia, at Brief Interview of Mental State (BIMS) show changes that put them in the level of moderate or severe impairment.

Cognitive changes may be associated with dementia or normal aging process. It was found that two-thirds of his sample had clinically definable cognitive impairment but they had no dementia (Graham et al., 1997).

This is a fact that happens repeatedly in nursing homes, and although in the study about 41.8% of the sample long-term care institutions showed cognitive impairment but not dementia. In their community sample, 46.3% of the subjects showed positive results for cognitive impairment (score <78 in Modified Mini-Mental State Examination) but they have the diagnostic category on clinical assessment of "cognitive impairment, no dementia" (CIDN).

Instruments

To assess the costs associated with dementia there are internationally defined protocols that include multiple dimensions.

These protocols are standardized into six dimensions, namely, (1) the use of emergency rooms and doctor's appointments, either in public or private institutions; (2) days of hospitalization; (3) medication; (4) social services use; (5) the need for technical support; and (6) the utilization of rehabilitation services (Ostbye and Crosse, 1994; Jönsson, 2004; Wimo et al., 2010). These were the six dimensions analyzed in this study. The RAI-RUG, indirectly, is an instrument used in this study.

Procedures

Data collection took place between February and May 2013. Data was collected retrospectively in a period of 12 months (January 2012 to January 2013), through access to institutional documents, including daily occurrences to account for the number of trips to the emergency room, appointments in public or private institutions, hospital stay days, and consultations in rehabilitation services. The cost of six dimensions were analyzed.

Emergency Rooms or Appointments, in Public or Private Institutions

In this dimension, there was found the number of times each user attended emergency department, hospital visits and consultations at the health center. Consultations in private hospitals were also considered. The calculation of each episode was done by multiplying the number of emergency episodes/consultations with the actual price of each episode.

Financial, values for each episode were obtained considering the actual prices of health care episodes provided under the National Health Service[1]. Each basic emergency episode was considered to have the value of €51. Medical consultations in hospitals or health centers have a cost of €31. Private consultations represent a real cost of €80.

Days of Hospitalization

To analyze the hospitalization costs, the number of days that each user was hospitalized in 2012 was recorded. These data were multiplied by the daily price of admission, a value of €85[1].

Medication

The value that the medication represents for the patient was analyzed through access to monthly medication receipts. It was considered the charged value. These receipts are issued independently of costs to the inpatient service in nursing home.

Social Services Used

All subjects included in the study were part of the social response nursing home. For the assessment of this dimension, the reference value with families in nursing home for the year 2012 was considered. This amount is €930.06/user/month (Ministry of Solidarity Employment and Social Security and Union of Portuguese Mutual Societies, 2011).

Technical Aids

The technical aids that each person used were checked with the staff and their price was assessed on commercial sites. The price of all technical aids used were considered. For technical aids with a long duration (such as beds and mattresses), however, we considered an amortization period of 8 years. To account for the cost of medical drugs and diapers (included under technical aids), the monthly bills of the subjects were acceded.

Rehabilitation Services

The number of sessions of physiotherapy, occupational therapy, podiatry or chiropractic treatments and the assistive devices used by the patients were checked in the records or with the institution's staff. Differentiation was made between the prices of physical therapy sessions in relation to the severity of dementia according to the stages defined by the BIMS in RAI-RUG. In this test, higher scores indicate cognitively intact and lower scores show severe impairment (Department of Health and Mental Hygiene, 2011).

With the results of this test, it was possible to classify subjects with three scores: (1) intact cognition, (2) moderate, or (3) severe impairment (Department of Health and Mental Hygiene, 2011).

It is considered that a physiotherapy session consists of three phases, (1) heating step, (2) training phase, and (3) relaxation phase. Using the assumptions presented above, a set of treatments that should be included in a physiotherapy session at each stage of dementia and for subjects without dementia were defined. The prices for each technique are the prices set by the National Health Service[1]. The value of a physical therapy session for a user without dementia was estimated at €26.40, €49.6 for the slight stage and €54.4 for the severe stage.

Because this is a relatively cheap service when compared with a doctor's appointment and its price is not well established, by generalizing the values of occupational therapy, it is considered that a physiotherapy consultation costs €22. For occupational therapy sessions a value of €22 per session was considered, regardless of the level of severity[1]. For sessions of podiatry and chiropractic the values that the user disbursed in private services were counted, as these treatments are not included in the National Health Service price list.

Statistical Analysis

Statistical analyses were performed using the program IBM SPSS version 19.0. The significance level $\alpha = 0.05$ was considered. Frequencies (absolute and relative) were used to provide descriptive statistics of the socio-demographic variables. Means and Standard Deviation (SD) were used to analyze the data dimension of economic costs. Univariable and multivariable general linear models were performed in order to assess associations between dementia costs and the characteristics of the subjects (RAI-RUG variables).

Were initially considered 400 variables of RAI-RUG in the model construction. Of all the variables included in the analysis, the total score was considered. Were included questions of these groups: (A) Identification Information (i.e., age, gender); (B) Hearing, Speech, and Vision (i.e., speech clarity); (C) Cognitive Patterns (i.e., temporal orientation); (D) Mood (i.e., Resident Mood Interview); (E) Behavior (i.e., psychosis); (G) Functional Status (i.e., bed mobility); (H) Bladder and Bowel (i.e., bowel continence); (I) Active Disease Diagnosis (i.e., heart/circulation, gastrointestinal, infections); (J) Health Conditions (i.e., pain management); (K) Swallowing/Nutritional Status (i.e., swallowing disorder); (L) Oral/Dental Status (i.e., broken or loosely fitting full or partial denture); (M) Skin Conditions (i.e., determination of pressure ulcer risk); (N) Medications (i.e., injections, insulin); (O) Special Treatments and Procedures (i.e., chemotherapy, dialysis); (P) Restrains (i.e., bed rall, trunk restraint) (Centers for Medicare and Medicaid Services, 2013). Pearson correlation was calculated with the objective of selecting the variables of RAI-RUG with the highest correlation with regard to the dependent variable (costs), being considered all variables with $p < 0.05$. Univariable logistic models were performed considering costs as dependent variables and each of the variables was significantly associated with the costs (26) found in the previous step. As a candidate for the multivariable model, we considered all variables significant at the 0.10 significance level in the univariable models. The final model includes all variables with $p < 0.05$.

Results

Costs Dimensions

The mean ± SD was used to provide descriptive statistics for economic costs (**Table 2**). Annually, a user with dementia in a nursing home displays an average cost of €15.3 thousand ($SD = 4021$), while a user without dementia presents an expenditure of

[1]Portaria n.° 132/2009 de 30 de Janeiro. *Diário da República, 1.ª série—N. ° 21.* Lisboa: Ministério da Saúde.

TABLE 1 | Socio-demographic information of the sample ($n = 72$) divided into two groups: with dementia ($n = 36$) and without dementia ($n = 36$).

Variable	With dementia ($n = 36$)	Without dementia ($n = 36$)	Chi-square	p-value
	n (%)	n (%)		
GENDER				
Male	6 (16.7)	19 (52.8)	10.356	0.001
Female	30 (83.3)	17 (47.2)		
AGE				
65–74	1 (2.8)	7 (19.4)	5.063	0.080
75–84	18 (50)	15 (41.7)		
> 84	17 (47.2)	14 (38.9)		
SCHOOLING				
<primary	24 (66.7)	23 (63.9)	0.061	0.804
≥primary	12 (33.3)	13 (36.1)		
MARITAL STATUS				
Single	5 (13.9)	8 (22.2)	1.969	0.579
Married	7 (19.4)	6 (16.7)		
Widowed	24 (66.7)	21 (58.3)		
Divorced	0 (0)	1 (2.8)		
HOSPITALIZATION TIME				
<1 year	20 (55.6)	21 (58.3)	0.072	0.965
1–5 years	11 (30.6)	10 (27.8)		
>5 years	5 (13.9)	5 (13.9)		
AMOUNT RECEIVED BY THE OWNER OF SOCIAL SECURITY				
<€445	20 (55.6)	28 (77.8)	4.000	0.046
≥€445	16 (44.4)	8 (22.2)		
STATE SEVERITY BIMS				
Intact cognition	1 (2.8)	18 (50)	27.300	0.000
Moderate	4 (11.1)	8 (22.2)		
Severe	31 (86.1)	10 (27.8)		

€12.3 thousand ($SD = 1288$), a difference of €3000 between the two types of subjects.

Social services are the largest share of the costs. The values of this dimension are the same for both groups, enough so that it is difficult to distinguish between them. In Portugal the financial support provided by the state is fixed, regardless of the economic situation and the degree of dependence of the user (Silva et al., 2015). However, at nursing homes, it can be given an additional value attributed by user in 2nd degree dependency situation (Silva et al., 2015). In the year of 2011–2012 this value was €65.35 per individual by month, and if the institution has more than 75% of users with this level of dependence was assigned an additional amount of €45.78 (Ministry of Solidarity Employment and Social Security and Union of Portuguese Mutual Societies, 2011).

For the dementia group, however, the use of social services represents 73% of the costs, while the same plot for subjects without dementia accounts for about 91% of the costs. After this portion, representing the largest volume in both groups are: rehabilitation services, technical aids, medication, hospitalization, and use of emergency services and hospital appointments at a private institution or a Health.

TABLE 2 | Economic costs by size and weight of the cost volume [mean (SD)].

Dimension	Average annual cost/user with dementia (€)	%	Average annual cost/user without dementia (€)	%
Emergency rooms or appointments, in public or private institutions	105 (123.8)	1	75 (80)	1
Days hospitalized	300 (571.6)	2	165 (336.3)	1
Medication	467 (518.4)	3	280 (273.7)	3
Social services used	11,161 (0.0)	73	11,161 (0.0)	91
Technical aids	651 (396.0)	4	138 (275.3)	1
Rehabilitation services	2604 (3773.4)	17	470 (1006.4)	4
Total cost	15,287 (4020.9)	100	12,289 (1287.8)	100

Except for the group without dementia, the size of the use of medication (with dementia: 467 €; without dementia: 280 €) takes up a larger volume than the use of technical aids (with dementia: 651 €; without dementia: 138 €). It should be noted that the size of technical aids includes the cost of diapers. The annual charge in diapers for the group with dementia was €19.5 thousand ($SD = 3709$), about 83% of the costs associated with technical aids. For the group of subjects without dementia, diapers accounted for about 69% of the cost of all technical aids.

Predictive Costs Model

In the univariable general linear models for each of the 26 variables analyzed, considering a $p < 0.1$, eight significant variables were obtained. There are three types of significant variables. First, there are the communication variables ("plainness of speech" and "ability to make yourself understood"). There is a known relationship between dementia and lower control capabilities in the areas of verbal expression, auditory comprehension, repetition, reading, and writing (Murdoch et al., 1987). Communication problems lead to behavioral changes (Horner, 1985). To monitor and prevent problems associated with behavioral changes, it is necessary to increase vigilance on the part of the auxiliary personnel, which increases costs.

The second type of variable is related to the Activities of Daily Living. In this model, three variables were significant "self-performance of Activities of Daily Living" including: "locomotion outside the institution," "dressing," and "personal hygiene."

The third type of variable is associated with the state of health concerning "thyroid disorders" and "risk for pressure ulcers." There is a correlation between the prevalence of pressure ulcers and certain diseases, such as dementia (Tsokos et al., 2000). The presence of problems with nutritional status, chronic diseases, changes in sensory perception, functionality, and the immobility of people with dementia increases their vulnerability

and likelihood of developing pressure sores (Oot-Giromini, 1993; Zekry et al., 2008; Jaul, 2010).

Preventing or reducing the likelihood of developing ulcers through methods such as frequent alternation decubitus, the use of specific support surfaces, or diapering in the case of incontinence and hydration, leads to an increase of time spent by the subjects with professionals, which translates into increased costs (European Pressure Ulcer Advisory Panel and American National Pressure Ulcer Advisory Panel, 2009). Thyroid clinical disorders are associated with cognitive disorders and dementia (Dugbartey, 1998). The costs associated with specific medication for this gland's problems were analyzed. All subjects take one pill per day, which represents an annual price of €43 (INFARMED, 2012) because there appears to be no specific medication for thyroid disorders, which increases costs. It was found, though, that the five subjects with thyroid problems combined to make a total of 56 days of hospitalization, which translates into €4760. Additionally, physiotherapy represented an annual cost of €24232, about €4846 per user. We could not clarify the origin of days of hospitalization and physical therapy sessions, but this may be the result of two factors. They may have arisen randomly, so there is not actually any link between the internment/physiotherapy and thyroid disorders, or in a spurious manner, in which there is a connection to the changes in the thyroid.

Other variables would also be expected to be significant. There may be several factors responsible for the insignificance of variables that would be expected as a result of the predictive variables costs. First, it is assumed that the groups can be very homogenous and there are no evident differences in the end. The fact stands that 50% of the subjects are members of the group without dementia, but the BIMS classify them as having moderate to severe cognitive impairment, which can also influence the results. As stated above this is quite common in nursing homes (Graham et al., 1997). The existence of only four individuals with moderate-stage dementia does not leave reliably comparable groups of people with dementia in the moderate and severe stages.

The eight variables of significance were entered into the multivariable general linear model (**Table 3**). Then the variables with the highest *p*-values were removed to obtain the final model (**Table 4**).

Individuals who are understood verbally influence lower costs as compared to subjects who rarely/are never understood. The subjects who rely totally on others to dress them positively influences costs and those who have thyroid problems exert a positive influence on increased costs. Considering the variables that make up the final model interactions between the three variables (two by two), predictive costs were also tested. Since none of the interactions proved statistically significant, it was decided to not include any of this information in the final model.

In models created the socio-demographic variables, as age and gender, were not found to be significant in the variable costs.

TABLE 3 | Multivariable general linear model of covariates and factors associated with economic costs ($n = 72$).

Variable	B (slope of the regression line)	95% confidence interval for B	Probability
CLARITY OF SPEECH			
Clear speech	644.796	−1637.536; 2927.128	0.574
Slurred speech/no speech	–	–	
ABILITY TO MAKE YOURSELF UNDERSTOOD			
Understood	−3294.063	−5843.691; −744.435	0.012
Rarely/never understood	–	–	
AUTO PERFORMANCE LOCOMOTION OUTSIDE THE INSTITUTION			
Independent	−303.109	−1922.075; 1315.857	0.192
Total dependence	−3447.875	−7337.208; 441.458	
Activity did not occur	–	–	
AUTO PERFORMANCE: PERSONAL HYGIENE			
Independent	−252.235	−2562.575; 2058.106	0.828
Total dependence	–	–	
AUTO PERFORMANCE: GETTING DRESSED			
Independent	−2,693.293	−5112.769; −273.816	0.030
Total dependence	–	–	
LIMITATIONS OF RANGE OF MOTION OF UPPER LIMBS			
No deterioration	665.716	−2732.800; 4064.232	0.116
Deterioration of one side	3551.739	−756.317; 7859.796	
Impairment of both sides	–	–	
DISTURBANCES IN THYROID			
No	−3292.521	−6448.073; −136.969	0.041
Yes	–	–	
RISK OF PRESSURE ULCERS			
No	−793.720	−4559.510; 2972.070	0.675
Yes	–	–	

Discussion

This study is the first in Portugal to analyze the direct costs of dementia in nursing homes. A user in a nursing home with dementia presents a cost of €15,287, about €3 thousand more than the cost of a user without dementia in the same service. The prevalence of people with dementia in the four non-profit organizations analyzed is 17%. The latest data shows that in 2010 about 66,275 people lived in nursing homes (Letra and Martín, 2010). At a rate of 17%, it estimated that in Portugal alone there exist 11,267 people in nursing homes with a diagnosis or signs of dementia. Given the figures, 11,267 diagnosed people represent an annual cost of €172 million. This represents 0.104% of the Portuguese GDP in the year 2012 (FFMS, 2013).

Given that there is no common methodology between the present and previous studies (Wimo et al., 2007, 2010), a comparison of data is not reliable, but it has been presented to verify discrepancies.

In 2005, the direct cost with 113,039 people was around €736 million (Wimo et al., 2007). Considering the values of the present study, with regard to 113,039 people, the costs would accrue to €992 million according to the value calculated (Wimo et al., 2007).

There are several alternatives to the institutionalization of a person with dementia that would result in lower annual costs than those that were found. We present three policies to support families in preventing hospitalization through specialization or a combination of services: the use of (1) day centers specific to

TABLE 4 | Final Model of covariates and factors associated with economic costs ($n = 72$).

Variable	B (slope of the regression line)	95% confidence interval for B	Probability
ABILITY TO MAKE YOURSELF UNDERSTOOD			
Understood	−2442.192	−4277.343; −607.040	0.010
Rarely/never understood	–	–	
AUTO PERFORMANCE: GETTING DRESSED			
Independent	−2477.784	−4161.358; −794.210	0.005
Total dependence	–	–	
DISTURBANCES IN THYROID			
No	−3197.691	−5,890.957; −504.425	0.021
Yes	–	–	

dementia, (2) home care services along with a location tracking device, and (3) respite care services.

Specific day centers offer appropriate care, therapies, and activities catered to their patients that stimulate their participation and integration. Private sector in Madrid has specific day centers for Alzheimer's disease and other forms of dementia. On average, the monthly payment can vary between €175 and €935 (depending on schedules and contracted services) (Maria Wolff Alzheimer, 2013[2]). Comparatively, a nursing home in Madrid has a monthly cost of €1790 (Inforesidencias, 2012).

The second hypothesis is the combination between a home support service and a location tracking device. The monthly amount considered for the home support service (maximum reimbursement for the home support service is expressed in the Protocol of Cooperation 2011–2012) is €239 (Ministry of Solidarity Employment and Social Security and Union of Portuguese Mutual Societies, 2011). In Portugal, the acquisition system for a portable locating device with GPS/LBS is around €150 for the equipment, plus a €20 monthly fee (Portuguese Red Cross, 2013). This combination of services represents an annual cost of €3284.

The last alternative is respite care services. The total cost of implementing a group psychoeducational intervention of 11 sessions with an average of nine participants per session is €4123 (Caravau et al., 2013). This amounts to around €458 per participant, with a payback period of 8 years at €5 per month.

The predictive model shows that only three of the variables led to increased costs of internment with subjects in nursing homes. Subjects who rarely or are never understood, those who need support in getting dressed, and those with clinical disorders of the thyroid are showing greater cost shares for inpatient care. It was appropriate that in future investigations were analyzed the relationship between the economic costs to the degree of dependence of the person. However, in this study was not possible to do so because it would be necessary to establish a minimum number of people for each group, about 20–30 people per group. There was no statistical capacity with this sample for this procedure.

The costs of caring for a person with dementia are high and represent a major burden on the economy of the country, patients, and families. Knowing the real costs of an individual with dementia in nursing homes allows for a more effective management and efficient use of national resources.

The present results may support the evaluation of the impact of policies, the prioritization of expenditures, and the adjustment of decisions based on the Portuguese reality.

Overall, it is believed that this study has obtained a good approximation of the actual costs of a user with dementia. Studies such as this should be applied at a national level to fully understand a panoramic view of Portugal, and in future research it would be interesting to analyze the cost that represented the use of social resources to the Government, to the patient and the family.

[2]Maria Wolff Alzheimer. (2013). Available online at: http://mariawolff.info/.

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frontiers in Aging Neuroscience

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The importance of neighborhood ecological assets in community dwelling old people aging outcomes: A study in Northern Portugal

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Human development is a bidirectional, person-context relational process, but scarce evidence is available about the relation between the individual variability across the life-span and the neighborhood ecological assets. Therefore, it is important that research focus not only on personal characteristics but on ecological assets as well. This way this study aims to analyze the association between neighborhood ecological assets categorized into four dimensions: human, physical or institutional, social or collective activity, accessibility, and the individual functioning. A 3% sample of residents aged 65 years and older in two downtown and three uptown parishes stratified by age and sex was interviewed at home using a protocol that included the Portuguese version of the Barthel Index in basic activities of daily living (BADL), the Lawton Instrumental Activities of Daily Living Scale (IADL), the Mini Mental State Examination (MMSE), and the Geriatric Depression Scale-15 items (GDS) for evaluating functionality, cognitive performance, and depression. The 162 participants were aged on average 75 years (sd = 7.0), 54% were women and 90% had less than 7 years of education. The majority of participants were independent in BADL ($M = 90$; sd = 17.7) and moderately dependent in IADL ($M = 13$, sd = 6.0), 20% showed cognitive impairment and a mean score of 8 (sd = 2.1) in GDS-15. After controlling for the effect of socio-demographic characteristics, functionality, and cognitive performance decreases in persons with worst outdoor mobility. On the other hand depressive symptoms are less common as the number of recreation opportunities, namely associative groups (cultural, educative, professional), increases. These results suggest that aging policies and practices must be ecologically embedded.

Keywords: ecological assets, activities of daily living, cognitive functioning, depression, aging outcomes

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Introduction

Currently, human aging is seen as one of the highest challenges of the XXI century. In the western world, we won about 33 years in average life expectancy, which rose from about 46 years, in 1900, to about 79 years in the end of the century (Walker, 2010; Hooyman and Kiyak, 2011). However, longevity advances are not being accompanied by a similar transformation in societal terms, leading Baltes and Smith (2003) to question our capacity to conciliate

longevity and dignity, especially in fourth age. Furthermore, considering the theoretical and methodological knowledge advance, in the Social and Behavioral Sciences, in terms of the *life course perspective, aging is a lifelong process*, situated in an historical space and time (Elder, 1974; Elder and Shanahan, 1998). Also, according to the *life-span developmental psychology* (Baltes, 1987, 1997; Baltes et al., 2006), development is not completed at adulthood (maturity); rather ontogenesis extends across life span. Thus, aging is a dynamic process of gains and losses, which follows from the biological and cultural architecture.

In the present study, we focused on the following aging outcomes: functional dependency, cognitive functioning, and depression. These outcomes have mostly been analyzed under a socio-demographic characteristics perspective. Functional dependency has been tightly associated to age, gender, education, and marital status. This way, dependent old people are mainly women, widows, people living alone and with low education (Murtagh and Hubert, 2004; Formiga et al., 2007; Santos et al., 2007; Espigares et al., 2008; Torres et al., 2009; Espigares and Torres, 2010; Espelt et al., 2010; Nunes et al., 2010). Functional dependency prevalence takes different shapes, as it refers to basic activities of daily living (BADL) or to instrumental activities of daily living (IADL). The majority of old people is independent in BADL (Costa et al., 2006; Schneider et al., 2008; Nakatani et al., 2009; Espigares and Torres, 2010) but those who are 70 or older are more prone to be dependent in IADL, and if they are older than 80 years, they might be dependent on both IADL and BADL (Nunes et al., 2010). Research has shown that both the prevalence and the rate of dependency increase with age (Espigares et al., 2008; Espelt et al., 2010) and that dependency is associated with several factors as cognitive impairment, depression, neurological diseases, back, neck and shoulders pain, osteoarthritis, chronic back problems, osteoporosis, more medication, lower economic resources (Murtagh and Hubert, 2004; Formiga et al., 2007; Santos et al., 2007; Schneider et al., 2008; Nunes et al., 2010). On the other hand age is not the most important factor for cognitive impairment measured by the Mini Mental State Examination (MMSE; Green et al., 2008; Karlamangla et al., 2009), but it has been found a global decline in cognitive functioning with age (Hooren et al., 2007; Bourne et al., 2010; Martínez-Vidal et al., 2011). Beyond age, other factors have been associated to cognitive decline in old people, as gender, marital status, education, social support network, socioeconomic status, and lifestyle (Hooren et al., 2007; Karlamangla et al., 2009). In general, a worse cognitive functioning is present in men, old people living alone or institutionalized, with a small social network confined to family, with little physical activity and having scarce socioeconomic and educational resources (Hooren et al., 2007; Green et al., 2008; Lindwall et al., 2008; Karlamangla et al., 2009; Oliveira et al., 2011). Although it is consensual that age brings a decrease in cognitive functioning, cognitive resources that are built in childhood and adulthood can prevent it or delay it (Yount, 2008). The other aging outcome considered in this study is depression, considered the most prevalent psychopathological disorder in old age (Seby et al., 2011). Depression has been related to several sociodemographic variables, such as age, gender, marital status, socioeconomic status, and education. Higher levels of depression occur mostly in old people aged 70 or older (Beekman et al., 2002; Chou and Chi, 2005; García-Peña et al., 2008), in old women (Copeland et al., 2004; McCusker et al., 2005; Tsai et al., 2005; García-Peña et al., 2008; Weele et al., 2009; Oliveira et al., 2011; Seby et al., 2011), old people living alone (Tsai et al., 2005; Oliveira et al., 2011; Seby et al., 2011), and old people with lower education and low socioeconomic resources (Tsai et al., 2005; Perrino et al., 2009; Akyol et al., 2010; Engmann, 2011). Besides the sociodemographic profile, other risk factors have been identified, such as previous history of depression, lack of social support perception, narrow social network, one or more physical diseases, adverse life events, poor quality of life perception, and lack of a regular spiritual practice (Copeland et al., 2004; Chou and Chi, 2005; Koizumi et al., 2005; McCusker et al., 2005; Tsai et al., 2005; Wilson et al., 2007; García-Peña et al., 2008; Akyol et al., 2010; Seby et al., 2011). The three analyzed dimensions in the present study – functionality, cognitive functioning, and depression – have a central role on aging, since they interact and influence each other, acting as roots for the successful or unsuccessful aging.

In a *developmental systems perspective*, Lerner (2002, 2012) has developed a series of studies about the positive development of young adults, highlighting the role of the "ecological assets," wherein "assets can be conceived of within individuals, in the physical space, and emerging in the dynamic between the two" (Theokas and Lerner, 2006, p. 62). Regarding the Study of Positive Youth Development, these authors (2006) proposed four classes of observed ecological assets to organize the actual resources and opportunities in the environments – human, physical or institutional, collective activity, and accessibility. The concept definition, according to the above mentioned authors are as follows: (1) *Human resources* are defined as the strengths, skills, talents, and facilities of people and as instantiated by the roles they have. The characteristics, activities, and behaviors of individuals provide a manifestation of the social norms of a particular context; (2) *Physical or institutional resources* are intended to document opportunities for learning, recreation, and engagement with individuals and the physical world around oneself and, as well, for providing routines and structure for individuals. At the *neighborhood level*, the presence of libraries, community centers, and cultural experiences that are within walking distance, or available through public transportation may increase their use and thus their potential benefits; (3) *Collective activity* is intended to document mutual engagement between community members, parents, youth, schools personnel, and institutions of society. These organizations, groups, or mutual activities represent the combined efforts and actions of different sets of individuals, documenting ties and networks of a community's associational life and the climate of the key context of development; (4) *Accessibility* intents to document the ability of residents to partake of human resources and resource opportunities in the context. Accessibility can be conceptualized and operationalized in multiple ways: (a) documents physical ease of access and can refer to the transportation capacity and hours of operation of local businesses, infrastructure, or cultural institutions in a local community; (b) can refer to the

potential of youth to interact with the adults in the setting or what is the ratio of adults to children in a given neighborhood or how long has a family lived in a neighborhood; (c) can refer also to the safety of the physical environment and free of dangers.

Given these results, what happens in the studies about aging? Aging is a process that implies a series of alterations in the biological, psychological, and social domains. The multiple profiles that can result from the several combinations occurring among these alterations make aging a multifaceted process, shaped by previous development and, in which the individual has a proactive role, in that, in the interaction with the environment, he can become his own aging's author. This way, different life styles in different environments result in different aging processes, which approach or distance themselves from active or successful aging. Researches on Environmental Gerontology (Wahl et al., 2012) made a first theoretical approach to the works of Lawton and the lifespan developmental perspective in a conceptual article that aims to guide future research agenda and propose theoretical propositions to an integrative model of Aging Well. Nonetheless, these theoretical propositions were only discussed in theoretical terms and not empirically tested. According to Dannefer (2003, 2009), over the course of life, people accumulate advantages or disadvantages that may optimize or limit the aging process.

In this context, we may ask: can the life-span developmental perspective using the methodology adopted by Theokas and Lerner (2006) contribute to a better understanding of aging in place? The aim of this study is to demonstrate that ecological assets are associated with aging outcomes, namely functionality, cognitive functioning, and depression, in an urban environment.

Materials and Methods

Participants

Sample size was estimated to be 3% of the resident population aged 65 years and older living in the five parishes/inner city of Viana do Castelo based on estimates of inter-census population for 2006, stratified by age and sex. The IPVC scientific committee approved the study and all persons willing to participate gave informed consent. Persons were interviewed at home by a trained researcher and a stakeholder (usually the priest or the president of the parish committee) in each parish indicated the first person to be interviewed. This person in turn pointed × persons, usually ranging from 4 to 10, and from them we randomly selected 50% to initiate the process. This can be viewed as cluster sampling with clusters with variable size.

Data Collection

The collected information included socio-demographic characteristics, person's daily functioning and household and neighborhood relationships. The Lawton instrumental activities of daily living scale (IADL-Lawton) was used to assess functionality, the MMSE for cognitive performance and the Geriatric Depression Scale (GDS) for depression. Ecological assets by parish included physical facilities (Elder and health facilities, nursing homes and culture/sports/recreation facilities among others) and social resources (Sports/cultural, health support associations, educative associations, and local/professional groups) based on a social diagnostic report of the City Council/Interparish committee (Relatório Social, 2008). Information focusing the resources and social necessities of each selected parish was analyzed. Accessibility indicators were based on the inter-census population estimates: dependency index (persons aged 65 years or more/persons aged 15–64 years), longevity index (proportion of persons 85 years or more among those aged at least 65 years), and characteristics of the public transport network based.

Data Analysis

After data description, involving personal, micro, and macro-environmental characteristics, downtown and uptown residents were compared using non-parametric tests, the chi-square for categorical variables and the Kruskal–Wallis for ordinal/discrete variables. Hierarchical regression models were used to analyze predictors of functionality (IADL-Lawton), cognition (MMSE), and depression (GDS). The first block included socio-demographic characteristics; a second block included household and neighborhood assets that were entered in the model using a stepwise procedure; in the same way a third and fourth blocks included ecological assets, namely physical and social community resources and accessibility. Since the distribution of the MMSE scores did not follow the normal distribution we used a transformed variable – the square root of the number of errors [$\sqrt{}$(30 – score in MMSE = number of errors; Jacquin-Gada et al., 1997)].

Results

A total of 162 persons were interviewed in the five parishes ($n = 85$ in downtown and $n = 77$ in uptown) and half of them are aged between 65 and 74 years old (**Table 1**). Most of them are women (54.3%). About 9.3% are illiterate, most are married (46.9%) or widower (40.1%). Overall 56.8% had blue collar occupations during their professional life, being this proportion higher among the uptown residents comparing to downtown ($p = 0.018$). Participants lived in the same parish for 63 years (sd = 31.5) and the majority considered to have good household conditions and a good relationship with neighbors (80.9%), being this proportion even higher among the downtown residents ($p = 0.035$). Overall 28.4% of participants report difficulties in outdoor mobility.

The MMSE scores were associated with age ($p < 0.001$) and there were significant differences between the youngest and oldest groups; the IADL-Lawton score increased with age and the eldest had a higher score than the remainder. The GDS score were associated with age ($p < 0.05$) and there were significant differences between the two younger groups (65–74 vs. 75–84).

Table 2 shows the physical, social, and accessibility resources by each parish in downtown and uptown. Downtown parishes have more physical resources for childhood/ adolescence, for education and more culture/sports and recreation facilities, as

TABLE 1 | Human resources and microenvironment accessibility resources.

Characteristics	Downtown ($n = 85$)		Uptown ($n = 77$)		All ($n = 162$)		Test (p)†
	n	%	*n*	%	*n*	%	
Socio-demographic characteristics							
Age *M* (sd)	74.5	(7.0)	74.6	(7.1)	74.6	(7.0)	
65–74	48	56.5	44	57.1	92	56.8	0.3 (0.9)
75–84	29	34.1	24	31.2	53	32.7	
85+	8	9.4	9	11.7	17	10.5	
Gender (% of women)	40	47.1	48	62.3	88	54.3	3.8 (0.051)
Education *M* (sd)	5.0	(3.4)	2.9	(1.4)	4.0	(3.0)	
0	5	5.9	10	13.0	15	9.3	23.4 (<0.001)
1–3	14	16.5	27	35.1	41	25.3	
4–6	49	57.6	40	51.9	40	54.9	
7+	17	57.6	0	0.0	17	10.5	
Marital status							
Married	41	48.2	35	45.5	76	46.9	
Widower	32	37.6	33	42.9	65	40.1	
Single/separated/divorced	12	14.1	9	11.7	21	13.0	0.5 (0.8)
Type of occupation							
White collar	28	32.9	11	14.3	39	24.1	8.0 (0.018)
Blue collar	44	51.8	48	62.3	92	56.8	
Household	13	15.3	18	23.4	31	19.1	
Household and Neighborhood							
Neighborhood stability* *M* (sd)	61.5	29.5	64.6	33.8	62.9	31.5	0.5 (0.5)
Good household conditions	75	88.2	61	79.2	136	84.0	2.4 (0.1)
Good relationship with neighbors	74	87.1	57	74.0	131	80.9	4.4 (0.035)
Difficulty in outdoor mobility	19	22.4	27	35.1	46	28.4	3.2 (0.1)
Outcomes							
Functionality in IADL (Lawton)	12.9	(5.6)	13.5	(6.0)	13.1	(6.0)	
Cognitive performance [Mini Mental State Examination (MMSE)]	26.5	(4.0)	24.9	(4.7)	25.7	(4.4)	
Depression [Geriatric Depression Scale (GDS)]	7.6	(2.0)	8.6	(2.0)	8.1	(2.1)	

**Lifetime lived in the neighborhood (%); †X^2 for categorical variables and Kruskal–Wallis for continuous variables.*

well as more sports and cultural groups and local/professional groups.

Concerning accessibility, downtown parishes have a higher number of Bus Transportation in their territory. Minimum frequency of bus lines is lower in a downtown and in an uptown parish. Both dependency and longevity indexes are higher in downtown parishes.

The hierarchical regression models of functionality (IADL-Lawton), cognitive performance (MMSE) and depression (GDS) including a first set of personal characteristics and a second set of ecological assets (stepwise inclusion) indicated that 37% of the variability in functionality on the IADL-Lawton is explained by socio-demographic characteristics (age and marital state), household/neighborhood characteristics (outdoor mobility) and accessibility (dependency index and longevity index; **Table 3**).

Having difficulties in outdoor mobility ($p < 0.001$) and living in a parish with a lower dependency index ($p < 0.05$) and a higher longevity index ($p < 0.01$) is related to a higher score in IADL-Lawton (indicating worse levels in functionality), after controlling for the effect of socio-demographic characteristics.

Overall 32% of the variance in the MMSE (number of errors) is explained by the inclusion of socio-demographic characteristics (age and education), household and neighborhood characteristics (outdoor mobility) and accessibility (dependency index). Having difficulties in outdoor mobility ($p < 0.05$) and living in a parish with a lower dependency index ($p < 0.05$) is related to a higher number or errors in MMSE, after controlling for the effect of socio-demographic characteristics.

A total of 18% of the variance in the GDS is explained by inclusion of socio-demographic characteristics (marital state) and social resources. After controlling for demographic characteristics, depression decreases with the number of social resources ($p < 0.05$).

Discussion

Considering the aim of this study we may conclude that cognition is more determined by sociodemographic characteristics rather than ecological assets, while variability in functionality is more linked to ecological assets, namely outdoor mobility and longevity index. As far as depression is concerned, the availability

TABLE 2 | Macroenvironmental physical, social, and accessibility resources by parish.

	Downtown		Uptown		
	P1	**P2**	**P3**	**P4**	**P5**
Physical resources					
Elder facilities	1	5	1	0	2
Health facilities	2	5	0	1	2
Resources for childhood/adolescence	1	10	2	1	3
Resources for education	6	8	2	4	6
Culture/sports/recreation facilities	4	5	0	0	0
Social resources					
Sports/cultural groups	21	39	7	5	13
Health support associations/groups	0	3	0	0	0
Educative associations/groups	0	1	0	0	0
Local/professional groups	6	8	0	0	2
Accessibility					
Population (%)	32 (19.8)	53 (32.7)	21 (13.0)	26 (16.0)	30 (18.5)
Public transportation (Bus)					
Number	1.8	2.75	1	1	1.25
Minimum frequency (minutes)	30	10	30	10	15
Dependency index	0.28	0.21	0.23	0.16	0.16
Longevity index (%)	8.9	10.4	8.4	6.6	9.8

Physical resources: elders facilities: nursing homes; day care; home care; health facilities: hospitals; health centers; resources for childhood/adolescence: home care centers, day care centers; resources for education: kindergartens; schools; culture/sports/recreational opportunities: library; museums; recreational centers; civic centers; associations of retired persons.

Public transportation number: 1 = 1 Bus line for 12 h; dependency index: persons aged 65 or more years/persons aged 15–64 years; longevity index: persons aged 85 or more years/persons aged 65 or more years.

of social resources seems to be the most important ecological asset for ameliorating depression.

With respect to sociodemographic characteristics, there are more women in all age groups, and this number increases as the age group also increases. Illiteracy and lower education are common, mainly, among older elderly, while medium and high education (4–10 years) are typical among younger elderly. The number of widows increases with age, while the number of married elderly decreases. In relation to occupations, most elderly were retired including all elderly aged 85 or older. This way, the sociodemographic profile observed in this sample meets the profile usually described in gerontological literature, a predominance of women, married or widowed persons, retired with no occupation and with low education (Araújo et al., 2007; Espigares et al., 2008; Torres et al., 2010).

The capacity to perform BADL, assessed by Barthel Index, was significantly different among age groups, wherein functional decline was more marked after 85 years of age. This result supports literature that presents a significant increase in dependency for BADL from the fourth age. Santos et al. (2007) found that the incapacity index, measured by Barthel Index, increased from 23,6%, between 60 and 69 years, to 35% between 70 and 79 years, and to 47,7% from 80 years. This steepest functional decline from 85 years old on can be explained, partially, by the fact that most elderly participants of this study are inactive. Furthermore, the literature in the field has shown that the increase of dependency in BADL with age stems from physiological changes and pathologies typical of the aging process (Murtagh and Hubert, 2004; Torres et al., 2010).

In our study, we found significant differences in functionality to IADL, measured by Lawton Index, among age groups. Specifically, there was a more marked decline from 80 years, being more expressive after 85 years old. This data matches those presented in literature which associates the increase in dependency to the increase in age and which shows that the functional decline in IADL is previous to the functional decline in BADL. So, relatively to IADL measured by Lawton Index, Torres et al. (2010) found statistically significant differences according to age group, wherein the elderly with more than 77 years old were more dependent than those with less than 70 years. In the same direction, Costa et al. (2006) and Nakatani et al. (2009) found that, although most elderly participants in their study were independent in BADL, most of them also presented some dependence in IADL. Likewise Nunes et al. (2010) observed that while the functional decline in BADL occurred, mainly, in elderly aged from 80, the functional decline in IADL occurred in elderly aged from 70.

Even in relation to functionality in IADL, the regression analysis showed the 15% of variability is explained by sociodemographic characteristics. Other studies also found that advanced age and lower education are independent factors related to functional dependency (Formiga et al., 2007; Espigares et al., 2008). However, in our study, when the ecological assets were included in the regression analysis, we found that along with sociodemographic characteristics, outdoor mobility explains 32%

TABLE 3 | Multiple regression models* for functionality, cognitive performance, and depression including micro and macro environmental resources.

Characteristics	Functionality	Cognition	Depression
Socio-demographic characteristics			
Age (years)	0.20[a]	0.04[b]	0.03
Male vs. Female	0.94	−0.25	−0.28
Education (years)	0.76	−0.07[c]	0.01
Married vs. others	−2.45[b]	−0.27	−0.95[c]
White collar vs. others	−0.30	−0.33	−0.67
R^2	**0.15**	**0.26**	**0.14**
Household and neighborhood			
Outdoor mobility (difficult vs. others)	4.73[a]	0.42[c]	
Household conditions (good vs. others)			
Neighbors relation (good vs. others)			
Neighborhood stability**			
R^2	**0.32**	**0.30**	
Physical and social resources			
Physical			
Social			−0.02[c]
R^2			**0.18**
Accessibility			
Public transport net (number)			
Dependency index	−25.1[c]	−4.50[c]	
Longevity index	0.77[b]		
R^2	**0.37**	**0.32**	

Setwise regression models: first block – human resources (all variables enter the model); variables in the next three blocks entered the model using a stepwise procedure; R^2: coefficient of determination; **Lifetime lived in the same house (%); [a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$; physical and social resources: sum of values in* ***Table 2**.*

of the functionality in IADL variability, and when the longevity index is included, this model increases the explanation to 37%. These results suggest that ecological assets should be considered both in the assessment and intervention programs that aim to prevent functional decline.

In what concerns cognition, measured the MMSE, we found statistically significant differences according to age. Specifically, cognitive decline is higher among those participants who are 80 years or older, being more expressive after 85 years. This result fits with several studies that show that there is a general cognitive decline with age, even though age is not the referred as the main factor (Hooren et al., 2007; Bourne et al., 2010; Martínez-Vidal et al., 2011; Oliveira et al., 2011). This cognitive decline can be explained, to a certain point, by the high rate of illiteracy and of lower education in the elderly aged 85 or more, and also by the high number of retired and inactive elderly within this age group. Therefore, the literature has shown, the higher the education level the better the cognitive functioning. This way, Hooren et al. (2007) found that people with higher education had a better cognitive performance, suggesting that this may be due to having greater reserve capacity. Also Bosma et al. (2003) showed that lower education and little cognitively stimulating jobs contributed to a higher cognitive decline. Beyond education and activity, other variables have been associated with cognitive functioning. Specifically, elderly receiving more social support (Bourne et al., 2010), with larger social networks (Holtzman et al., 2004; Green et al., 2008) and married (van Gelder et al., 2006; Karlamangla et al., 2009) had lower cognitive decline. In this study, beyond the 26% of variability in cognitive performance explained by age and education, household and neighborhood indicators, namely outdoor mobility increases the explained variability to 30%, and accessibility indicators provide a further increase to 32%. Again, ecological assets seem to play an important role in cognitive functioning and so they should be included in planned proactive actions for community dwellers.

Concerning depression, there were no significant differences according to age, which is congruent with the literature in the field (Copeland et al., 2004). However, there are higher depression rates from 80 years of age on, which are congruent with the literature showing an increasing trend in depression with age (Beekman et al., 2002; Oliveira et al., 2011). This increase may be related, in this study, to the functional and cognitive decline and to a lesser availability of social resources, diminishing the opportunity for social interaction. Moreover, in the studies of Lenze et al. (2005) and Nunes et al. (2010), depression was a risk factor for incapacity and dependency. Other studies have reported an association with other variables, such as being female (Copeland et al., 2004; McCusker et al., 2005; Tsai et al., 2005; Weele et al., 2009; Oliveira et al., 2011; Seby et al., 2011), low education and socio-economic resources (Tsai et al., 2005; Akyol et al., 2010; Engmann, 2011), living alone (Tsai et al., 2005; Oliveira et al., 2011; Seby et al., 2011), low emotional support (Koizumi et al., 2005), and suffering physical diseases (Oliveira et al., 2011). In the present study, the sociodemographic variables, namely marital status, explain 14% of the variability in depression. However, when the ecological assets are included in the regression analysis, namely social resources the variability explained increases to 18%, suggesting that as the number of leisure opportunities increases depression decreases. These results are relevant because they show that ecological assets, specifically the leisure opportunities, should be integrated in proactive interventions in this field.

Alongside with works of Lerner (Theokas and Lerner, 2006; Urban et al., 2009) regarding the extent of a youth positive development associated with ecological assets, this is the first study showing that besides the acknowledged contribution of sociodemographic variables for aging outcomes, neighborhood ecological assets may have important contributions for ameliorating outcomes such as IADL, cognitive performance and depression in community dwelling old people. Considering the aim of this study we may conclude that cognition has a stronger association with sociodemographic characteristics rather than with ecological assets, while variability in functionality is more linked to ecological assets, namely outdoor mobility and longevity index.

As far as depression is concerned, the availability of social resources seems to be the most important ecological asset for ameliorating depression. Aging policies and practices should account for these aspects and be ecologically embedded.

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GENERAL COMMENTARY
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Commentary: "Mental distress in patients with cerebral visual injury assessed with the German Brief Symptom Inventory"

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Keywords: mental disorders, cerebral visual injury, adjustment to disease, mental distress, visual field defects

A commentary on

Mental distress in patients with cerebral visual injury assessed with the German Brief Symptom Inventory
by Gall, C., Brösel, D., and Franke, G. H. (2015). Front. Aging Neurosci. 7:51. doi: 10.3389/fnagi.2015.00051

Visual disorders are associated with a substantial economic and personal burden (Rein, 2013). The recent paper by Gall et al. (2015) examined the influence of visual disorder on one aspect of this burden, mental health. Their study involved 122 participants (mean age = 58.1 ± 15.6 years, 72 males, 61% either married or in a relationship) who had visual field defects associated with cerebral visual injury due to either optic neuropathies or postchiasmatic lesions following ischemic or hemorrhagic stroke. About one-quarter of the participants also had additional impairments, such as hearing loss ($n = 19$), tactile paresthesia ($n = 7$), and loss of sense of smell ($n = 5$). Their paper highlights the importance of clarifying the mental health challenges associated with eye diseases, such as macular degeneration and diabetic retinopathy (Mathew et al., 2011). Conceivably, it would not be at all surprising if many people become highly distressed and depressive after receiving such a diagnosis. Concern and anticipation about one's future health, social relationships, work status, and financial security would naturally increase, given expected increased difficulties with daily living and resultant deterioration in quality of life that such diseases can produce (Gall et al., 2015).

Gall et al. (2015) argue that the mental health impacts of cerebral visual injury, a result of optic neuropathies or lesions following ischemic or hemorrhagic stroke, is under investigated, and so requires clarification. To assess mental health, the investigators employed the brief symptom inventory (BSI), a well-validated psychometric tool that assesses domains, such as depressive mood, anxiety, hostility, and interpersonal sensitivity (Franke, 2015). Participants who were listed on a clinical database were invited to complete the BSI in addition to socio-demographic information. Cross-sectional mental health data on levels of psychological distress in the participants were compared to community norms for the BSI. Their findings indicated that cerebral visual injury is associated with elevated rates of mental health problems and concerns. For instance, they found over 25% of their sample reported clinical levels of psychological distress. While the cross-sectional nature of their study does not allow the conclusion of causal relationship, the most likely explanation is that the visual disorder leads to physical, social, behavioral, and personal anxieties and apprehensions, with the eventual possibility of leading to mental disorders like major depressive disorder. Similar dynamics have been shown to be associated with a number of physical disorders and diseases. For example, adults with a fluency disorder (chronic stuttering), a neurologically inherited disorder

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of communication, have been shown to be higher at risk of social anxiety disorder and elevated psychological distress including depressive mood and anxiety (Blumgart et al., 2010; Tran et al., 2011).

Furthermore, Gall et al. (2015) also found that participants with multisensory impairment (that is, visual impairment as well as impairment of other senses, such as smell and hearing) had significantly elevated levels of mental distress compared to those with visual impairment alone. This again is not surprising, and is not dissimilar to what we see with other physical disorders, like for instance, in people sustaining an acute spinal cord injury as well as a co-morbid traumatic brain injury (Craig et al., 2013, 2015). Gall et al. (2015) also suggested that quality of life will improve should mental health problems be addressed. This is certainly a positive way forward when dealing with impairment that is difficult to treat or perhaps not reversible. Arguably, assisting the person with the impairment to be more resilient by teaching skills designed to improve the way they cope and adjust with their disorder and impairment will prove to be a very attractive strategy. While the research findings of Gall et al. (2015) may seem evident, their data showing a strong connection between mental distress and a disorder like cerebral visual injury is highly important for directing future research in the area.

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Dual sensory loss and its mental health impacts: where to now?

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Keywords: dual sensory loss, older adults, mental health, clinical practice, multidisciplinary approach

A commentary on

Mental health and dual sensory loss in older adults: a systematic review
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It is common for older people to experience deterioration of their vision or hearing as they age. The combined effect of vision and hearing loss [known as Dual Sensory Loss (DSL)] is prevalent in the older adult population, occurring in up to 69% of adults aged 65 years and over (Wittich et al., 2012). Concomitant with this impairment is the risk of diminishing physical and mental health (Kiely et al., 2013), decreased communication interactions (Heine and Browning, 2002), and social isolation (Brennan et al., 2006). As eluded in the Heine and Browning (2002) article, in people with DSL, mental health consequences including depression, anxiety disorders, and cognitive aging have not been thoroughly and systematically investigated contributing to a sparse literature on which to base clinical practice.

The issues that arise are: what barriers impede early diagnosis and management of DSL and its mental health impacts, and how are these conditions identified and managed in clinical practice?

The identification of DSL is complicated especially since older adults often acquire this disorder slowly as they age, making DSL difficult to detect particularly in its mild form in either or both of the sensory domains. The research also supports the notion that older people with unisensory loss and those with DSL are not affected by the same impacts, and may not seek or need the same assistance especially if DSL is not identified at the time that unisensory loss is identified. McDonnall (2009) investigated the effect of DSL on depressive symptoms and whether people with DSL were more likely than those with a single sensory loss to experience depressive symptoms. The results of this study suggested that older adults with DSL were likely to experience symptoms of depression similar to those participants with vision loss, but significantly more likely to experience symptoms of depression than participants with hearing loss only. The impacts of unisensory loss and DSL also vary over time. Outcomes of a longitudinal study conducted by Brennan et al. (2006), suggested that in older adults, at baseline, DSL was associated with higher levels of functional disability compared to those adults with unisensory loss; however, the effect gradually diminished over time. These studies highlight the need for professionals to be vigilant in the detection of DSL and not overlook the possibility of an older adult having DSL even if they present symptoms in only one of the domains of vision or hearing loss.

For older adults themselves, numerous barriers to seeking assistance for their sensory losses may exist. It is common for older adults (especially those with DSL) to experience a range of physical and mental health conditions as they age. For example, Crews and Campbell (2004) found that older people with DSL are 2.4 times more likely to report heart disease, 3.6 times more likely to have reported a stroke, and 2.7 times more likely to report depression. It is thus possible that for older adults with DSL, their sensory loss may take on less importance as a priority compared to the other health conditions that may exist co-morbidly. For those with DSL, examples of further barriers preventing health seeking behaviors may include reduced mobility and independence and increased depression (Crews and Campbell, 2004; Brennan et al., 2006).

Vision and hearing health services are usually one-dimensional and the vision or hearing service provider may not be aware of the need for multidisciplinary collaboration. Although separate vision and hearing screening guidelines exist in the US (see U.S. Preventive Services Task Force, 2009, 2012), these are not necessarily adopted in other countries, do not cover DSL, and do not include screening for possible impacts of DSL such as mental health. One example of a multidimensional approach is the Joint Commissioning Strategy for People with Sensory Impairment 2011–2015 proposed by the Surrey County Council, UK[1]. This strategy includes increasing awareness of DSL, ensuring services for this population group meet their complex needs (for example, older adults with DSL and dementia)

[1]https://www.surreycc.gov.uk/__data/assets/pdf_file/0004/482557/Summary-version-Sensory-impairment-commissioning-strategy-v1.pdf

and that suitable services are offered for those with DSL.

Since DSL and its impacts cross numerous domains, the pathway for service provision is unclear. Professionals are thus encouraged to extend their skills to be able to screen for both sensory losses and identify associated impacts (such as depression and social isolation) so that appropriate referrals can be made. Multidisciplinary collaboration in the management process is necessary so that the best outcome can be achieved for those with DSL (Heine et al., 2002).

In order to encourage optimal mental health, successful aging and sustain quality of life for older adults with DSL, appropriate identification and effective management of older people with DSL is essential. In this regard, a number of points are highlighted including lack of credible and representative research investigating the impacts of DSL on mental health, guidelines regarding pathways for diagnosis and management of DSL in general and more specifically in those with mental health issues, and collaboration among the numerous professionals working in this field including medical and allied health professionals such as medical practitioners and specialists, audiologists, optometrists, and psychologists.

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Response: "Commentary: Mental distress in patients with cerebral visual injury assessed with the German Brief Symptom Inventory"

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Keywords: mental health, quality of life, cerebral visual injury, coping with disease, mental distress, visual field defects

A response to

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In his valuable commentary on our recent publication Ashley Craig pointed out that the observed "strong connection between mental distress and a disorder like cerebral visual injury is highly important for directing future research in the area." Within this context we wish to emphasize another significant factor: patients' quality of life that may be relevant as a potential mediator variable.

Besides generic health-related quality of life, vision-related quality of life as assessed with questionnaires such as the National Eye Institute—Visual Functioning Questionnaire (NEI-VFQ, Mangione et al., 2001) are important factors that may help to explain why some patients develop mental health impacts after cerebral injury while others do not. The NEI-VFQ may be used to gather information on how patients with visual field loss after lesions to the visual pathway are able to *cope* with daily visual tasks. For brain-damaged patients the NEI-VFQ may be ideally conducted together with a neuroophthalmological supplement which is available in English and German (Raphael et al., 2006; Wagenbreth et al., 2011).

Recently, we have observed that a higher extent of vision-related quality of life in patients with cerebral visual injury was related to lower levels of mental distress (Gall et al., 2013). We further hypothesized that the maintenance respectively elevation of vision-related quality of life could reduce and prevent mental distress due to vision problems. Thus, patients with persisting visual field defects may benefit from rehabilitation aiming at the development of individualized coping strategies. With a greater repertoire of coping strategies for visual demands in everyday life vision-related quality of life is likely to increase which may eventually translate into improved mental health.

Dr. Craig also highlighted the other side of the hypothesis, i.e., that "quality of life will improve should mental health problems be addressed" (Gall et al., 2015). In fact, it is very probable that the respective interventions—of which too few are being made available to visually impaired patients in need—may have a positive influence on both mental health and quality of life.

As pointed out in the commentary, very similar phenomena of elevated mental distress have been observed in patients with physical disorders after damage to the central nervous

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system (Craig, 2015). A next step forward may be to go beyond a cross-sectional methodology in order to study the occurrence of mental health problems with an economic questionnaire approach in longitudinal studies, for instance using the *Brief Symptom Inventory* (BSI, Franke, 2000), together with disease-related quality of life instruments, e.g., in post-stroke patients who likely suffer from sensory and physical symptoms at the same time. For the patients' benefit these studies should comprise an interventional approach targeting either neurological rehabilitation including designated coping strategies and/or psychotherapeutic interventions.

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