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Cognitive reserve and resilience in aging

Edited by
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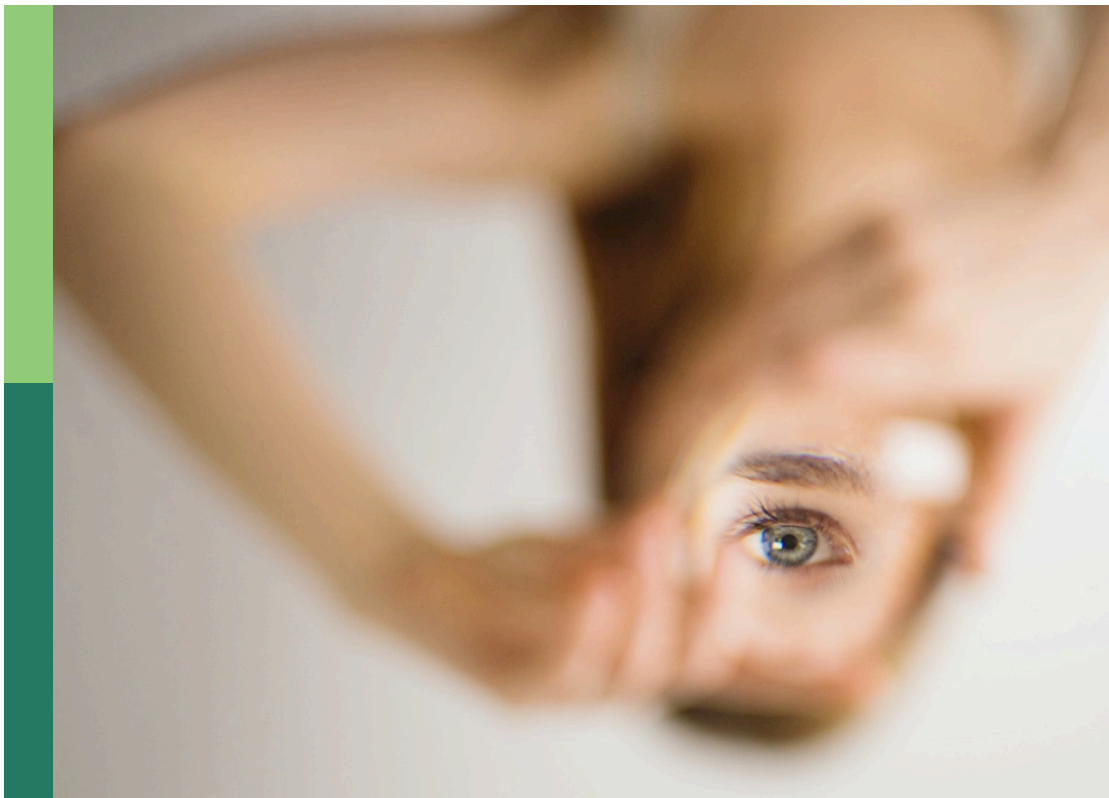

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Cognitive reserve and resilience in aging

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Editorial: Cognitive reserve and resilience in aging

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Editorial on the Research Topic
Cognitive reserve and resilience in aging

We are delighted to present the nine articles that compose this Research Topic. Consensus operational definitions for concepts of Cognitive Reserve (CR), Brain Maintenance (BM) and Brain Reserve (BR) were recently established by the NIH-funded Reserve and Resilience Collaboratory (https://reserveandresilience.com/). The overall term "resilience" was suggested to encompass all three concepts. The authors adhere to these operational definitions, which increases the clarity and applicability of their findings.

Both CR and BM can be influenced by genetic factors and lifetime exposures. Several papers focused on the nature of these exposures.

Multiple life experiences can be associated with increased CR. Nogueira et al. conducted a systematic review of the most used quantitative measurement methods for CR for in aging. They established that there is no gold standard tool incorporating all proxies and cognitive tests, and highlight the need to develop a more holistic battery for the quantitative assessment of CR.

Rather than reductionistic concepts of simple experiences contributing to reserve, Kempermann proposed a conceptual framework of the "embodied mind in motion", which recognizes that individual lifestyle is a complex composite of variables relating to both body and mind as well as receiving input and generating output. Hiking, playing musical instruments, dancing and yoga are presented as examples of body-mind activities which be associated with late-life resilience. The article, stresses the concepts of wellbeing and quality of life as drivers of successful interventions, and offers an access point for unraveling the mechanistic complexity of lifestyle-based prevention, including their (neuro-) biological foundations.

Regarding factors that may contribute risk for dementia, Vassilaki et al. present a new tool, the area deprivation index (ADI), which encompass geographic area-based estimates of the socioeconomic disadvantage of neighborhoods, and captures multifactorial contributors to the risk of dementia. They suggest possible mechanisms through which ADI may have an impact on Alzheimer's disease and related dementia outcomes, as well as how resilience can be improved over the lifespan in this context.

by considering the ADI as a modifiable risk factor, amenable to policy changes that can affect communities.

Another set of articles investigate CR and BM in the context of their contribution to cognition in the presence of age or disease related brain changes. The studies adhered to the Framework's operation definitions of these concepts. In particular studies of CR incorporated a brain change that results in cognitive change, and a potential moderator of this relationship.

Brichko et al. examine the association of a composite score, composed of years of education, literacy, and vocabulary measures, to the level and rate of change in white matter microstructure, as assessed by diffusion tensor imaging measures. In late middle-aged adults, their composite score was associated with more intact microstructure, consistent with the concept of BM. However, in their older participants, higher composite scores tended to be associated with reduced white matter integrity, suggesting that they contribute to CR by allowing these individuals to maintain cognitive performance in the presence of poorer WM integrity.

Cattaneo et al. investigate a measure of psychological wellbeing, the Sense of Coherence, as potential source of CR. Controlling for brain integrity, as measured by neuro-filament light chain measures, they found that this construct mediated the protective effect of more standard CR proxies on cognitive functions.

Kleineidam et al. explore the potential association of occupational cognitive requirements (OCR) in midlife with BM, brain reserve (BR), or CR. The results support the link between OCR and CR. For example, high OCRS was related to the association between carrying an APOE-ε4 allele and the observed cognitive decline, and it was associated with a later onset but subsequently stronger cognitive decline in individuals converting to dementia.

Böttcher et al. investigate the association and interplay between musical instrument playing during life, multi-domain cognitive abilities and brain morphology in older adults. Participants reporting long-term musical activity during life were compared to controls without musical activity well-matched for reserve proxies of education, intelligence, socioeconomic status and physical activity. Those with musical activity outperformed controls in global cognition, working memory, executive functions, language, and visuospatial abilities, and showed a stronger association between gray matter volumes and cognitive performance than controls.

Jauny et al. synthesize the current state of knowledge from MEG (magnetoencephalography) and EEG (electroencephalography) studies that investigated the contribution of maintenance of neural synchrony and variability of brain dynamics to both cognitive changes associated with healthy aging and the progression of neurodegenerative disease such as Alzheimer disease. They found that both maintenance of young-like synchrony as well as and compensatory adjustments appear to be related with to brain reserve. However, increased synchrony was deleterious in pathological aging.

Habeck et al. evaluated young and old participants during the maintenance phase of a verbal Sternberg fMRI task to identify multivariate activation patterns that increased expression with increased task load. Controlling for structural brain integrity, the load-related increases related *negatively* to mean task accuracy and neuropsychological functioning in the younger group, but positively in the older group. Further, when they prospectively applied the young-derived activation pattern to the older group, the resulting mean load-averaged pattern scores displayed positive correlations with mean task accuracy and neuropsychological functioning. Thus this activation pattern can be considered an implementation of CR.

Overall this set of studies makes a strong contribution to the methodology for studying BM and CR, as well as to potential functional mechanisms that may underly them. We hope that the ideas presented inspire further research in this important area.

Author contributions

RK wrote the first draft of the editorial. YS, DB-F, and RF edited the editorial. All authors contributed to the editorial revision, read, and approved the submitted version.

Conflict of interest

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.

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Embodied Prevention

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Evidence-based recommendations for lifestyles to promote healthy cognitive aging (exercise, education, non-smoking, balanced diet, etc.) root in reductionistic studies of mostly physical measurable factors with large effect sizes. In contrast, most people consider factors like autonomy, purpose, social participation and engagement, etc. as central to a high quality of life in old age. Evidence for a direct causal impact of these factors on healthy cognitive aging is still limited, albeit not absent. Ultimately, however, individual lifestyle is a complex composite of variables relating to both body and mind as well as to receiving input and generating output. The physical interventions are tied to the more subjective and mind-related aspects of lifestyle and wellbeing in the idea of the "embodied mind," which states that the mind is shaped by and requires the body. The causality is reciprocal and the process is dynamic, critically requiring movement: the "embodied mind" is a "embodied mind in motion." Hiking, playing musical instruments, dancing and yoga are examples of body–mind activities that assign depth, purpose, meaning, social embedding, etc. to long-term beneficial physical "activities" and increase quality of life not only as delayed gratification. The present motivational power of embodied activities allows benefiting from the side-effects of late-life resilience. The concept offers an access point for unraveling the mechanistic complexity of lifestyle-based prevention, including their neurobiological foundations.

Keywords: reserve, resilience, plasticity, maintenance, dementia, embodiment, walking, exercise

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INTRODUCTION

Aging confronts us with the gradually intensifying experience of how closely body and mind are entangled. What early in life appears a self-evident unity becomes increasingly fragile, when damages and other changes accumulate and the integrity of the mind–body-system is challenged (Kuehn et al., 2018). Dementias, as the extreme, are experienced as a loss of the self. In contrast to the broadly promoted, yet reductionistic strategies for healthy or "successful" cognitive aging (World Health Organization, 2019; Livingston et al., 2020), improved approaches should thus aim at maintaining the "embodied self" in a state that is able to master the challenges of an ever-increasing lifespan. If body and brain change, so does the mind, but their relationship, reflecting the duality of human nature, is far from linear or uniform and not the consequence of simple, accessible causalities.

This insight is not new: the "body and mind problem" continues to be an unresolved challenge to human self-reflection and philosophy. That over millenia the problem has not found a straightforward solution, might also be one reason, why lifestyle interventions that target body and mind separately,

fail to unequivocally reach us. While official health recommendations often do imply the existence of a causality from body to mind ("take the stairs and eat your beets" in order to "stay cognitively fit"), this link remains mechanistically vague and the existence of reverse causalities from mind to body is much less emphasized.

This article here explores, also from a neurobiological perspective, some challenges and chances that arise from the fact that body and mind are two undividable aspects of what and who we are, inseparable and not reducible to either of them. Hiking, playing a musical instrument, dancing and Yoga are discussed as exemplary activities and life-style activities that might guide the way for future approaches to healthy and successful cognitive aging that include this perspective. They are examples of complex body–mind activities that emphasize the emergent center that remains untouched by more reductionistic health behaviors. The key to understanding their particular nature and benefit lies in the idea of the "embodied mind." This concept has an undervalued neurobiological core that would allow to apply the tools of modern neurobiology to the question of how we can achieve and improve prevention.

The idea developed in this article is, however, explicitly not meant as argument against evidence-based recommendations and rigorous standards in scientific studies on identifiable life-style factors [as summarized, e.g., here: Livingston et al. (2020)], which remain necessary and important, but as a complementary perspective that can help to close a conspicuous gap.

It is acknowledged that the present hypothesis article takes a reductionistic approach in that many terms (mind, embodiment, wellbeing, plasticity, etc.) are taken at face validity, although relevant discussions about their exact meaning in this context should be led. The article also assumes a bird's eye perspective on the psychological, medical and neurobiological literature of lifestyle and lifestyle interventions, including the relevant methodology. For the time being we are not considering many details that ultimately will become relevant. The article is not meant as last word on the proposed concept but rather as an invitation to discuss the idea in an interdisciplinary field. A more in-depth elaboration, including methods, concrete directions of future intervention studies and a more formalized model will have to follow.

THE EMBODIED MIND IN MOTION

"Embodiment" in the sense applied here stands for the "*seemingly simple idea that intelligence requires a body*" and that "*not only categorization is grounded in (shaped by) the body, but so is cognition in general, including spatial and social cognition, problem solving and reasoning, and natural language*" (Pfeifer and Bongard, 2006). The concept of embodiment, which originated in both philosophy and cognitive neuroscience has many facets (Meteyard et al., 2012), the key point here being that, irrespective of details in the conceptualization, the brain is not isolated from the body, as the nervous system with both afferences and efferences permeates every bit of it structurally and functionally.

While the "self" is a construct built by the mind, it is inseparable from our bodily existence. The bodily boundaries, densely equipped with sensory receptors, are the relevant interface to the world. Communication with the world happens here, not at the meninges (as the boundaries of the brain) or an ephemeral "soul." So close is the link to outer experience that virtual reality can, at least on the short term, trick us into illusionary body experiences (Landau et al., 2020).

The body is also the sole reference framework for perception and action that is stable throughout life. Consequently, across our lifespan, we perceive ourselves as living in the same body, even though, objectively, this body changes substantially over the years. But our intuitive self-experience is a unity of the "I" and its body. This is, as pointed out by G.F. Stout, either a fundamental illusion, or must become the basis of all our attempts to the determine the relation of body and mind (Stout, 2012). This is also of relevance when we attempt to increase resilience of brain and mind through bodily interventions, which is the most common idea behind lifestyle-based prevention. But in its unidirectionality this can be clearly only part of the full picture.

For prevention of cognitive decline, we need to target body and mind as entwined, not as separate entities. Again, this is not to say that individual measures, e.g., to promote exercise or balanced diets are not useful, but that by themselves they have limitations that could be overcome with more holistic approaches.

LIMITS OF CONVENTIONAL PREVENTION CONCEPTS

Lifestyle interventions to prevent cognitive decline have proven effectiveness (Kivipelto et al., 2018). It is thus for plausible reasons that the WHO, the Lancet Commission and other institutions base their recommendations on best evidence from epidemiological and intervention studies (World Health Organization, 2019; Livingston et al., 2020). However, this approach, while scientifically and ethically correct, is inevitably not only biased to what could already be studied appropriately but also blind to many interaction effects. In addition, it ignores the large number of additional small factors that sum up to a substantial proportion of the observed or theoretically possible effect, even though they individually fail to reach statistical significance.

Finally, and most importantly, the conventional single factor approach favors easily quantifiable measures that are conceptually straightforward, usually at a physical level, over the complex, supposedly "soft" measures that require the problematic assessment of values, purpose, and social interactions. In contrast, most people value the latter much more highly than the former and intuitively place the plain activities into their larger "softer" contexts. 'Diet, for example, is not just "nutrition" and the appropriately measured intake of calories, but ideally a broadly fulfilling and highly social activity.' What comes to mind with "Mediterranean diet" is not just a balanced list of particular healthy ingredients, but an approach to life in a much broader sense, ranging from taste to associations of southern life, that

defies the reductionism into which it is squeezed. Consumption of the ingredients as such will to some degree be beneficial as preventive practice (Valls-Pedret et al., 2015), but its acceptance will ultimately depend on the experience of the beneficial connotations that are hard to capture in rigorous scientific studies but whose emotional value might be the most potent driver of health behaviors.

The important non-physical lifestyle factor "education" might at first appear to be an exception of this rule, but in most studies education is not captured as a continuous lifelong activity but as past "educational attainment," often equal to the highest school degree obtained. The complex dynamic process is reduced to a single number or category. Nevertheless, the early-life academic achievement, independent of any continued education, provides an offset for down-ward sloping cognitive trajectories but does not further flatten the slope of the decline (Nyberg et al., 2021). While this offsetting reserve-like effect is important, the educational foundation that is laid in the past does not necessarily reflect learning-related lifestyles later in life. An interaction effect of continued education with the cognitive trajectories is much more difficult to assess. One attempt has been made in a large study showing that participation in intellectual activities late in life is still associated with a lower risk of incident dementia years later, independent of other lifestyle factors (Lee et al., 2018).

Some attempts have also been undertaken to address the subjectively very highly valued but even more elusive forces such as religious practice, volunteering, optimism, etc. [see Table 1 in Kempermann (2019b)]. Nevertheless, there are some suggestive indications of their positive effects on cognitive aging—not unexpectedly though with by and large weak evidence. Such studies usually rely on self-reports, are burdened with numerous risks of bias and tend to suffer from poor quantifiability. In the end the "immaterial" aspects thus usually remain problematically lifeless and abstract. To overcome this problem, it might be more promising to leave the box closed and assess complex lifestyles as a whole, forfeiting the ambition to isolate relevant ingredients but come to more relevant conclusions about practices that are bundled in real-life anyway.

THE NATURE OF LIFE-STYLE AND LIFE-STYLE-BASED INTERVENTIONS

Lifestyle-based interventions literally aim at intervening at how people decide to live their lives and how they actually enact that explicit or unconscious decision. They thus require a broad understanding of "lifestyle" itself.

- Lifestyles are stable yet highly personal and individual patterns. How an individual leads his or her life, is expression of personal preferences and shaped by experience. Standard recommendations for healthy lifestyles can only generically address facets of this complexity. Two key scientific questions arise: What are cause and consequence of the inter-individual variability? And what, on the other hand, is the common ground between individuals?
- Personal lifestyles are shaped by gene × environment interactions like all other traits. The genetic component must not be neglected. Environment importantly includes the non-shared factor of individual activity and behavior that is critical for lifestyle interventions to support lasting health. The key scientific question is how this individualizing phenotypic complexity might be captured, modeled and analyzed.
- Lifestyles are about wellbeing in the presence. What we accept as "good for us" is only to a small part governed by rational decisions and the expectance of delayed gratification. Lifestyles are also subjective with respect to the quality of the experience and the assigned emotional value. The question is how individual wellbeing as a state of balance is a consequence of lifestyle (and its conscious changes).

PHYSICAL ACTIVITY AS A COMMON DENOMINATOR

Given the obvious complexity it has always puzzled people that among the identifiable components of lifestyle, plain physical activity appears to play a dominating role (Norton et al., 2014). Ultimately this might not be so surprising, however, as nervous systems have evolved to allow active mobility and as all output of the brain is ultimately motoric. Physical activity immediately engages the brain on both the input and output side. Physical activity is a motoric output of the brain that generates sensory input, both from the body itself and environment. The intrinsic feedback happens directly through efference copies and indirectly measuring the effects in the periphery.

Proprioception and balance provide constant and massive input from the moving body to the brain. In addition, rhythms of neural activity resonate with patterns of physical movement, such as during walking, and promote theta rhythms in the hippocampus, which facilitate memory consolidation (Terrazas et al., 2005).

It is therefore plausible that all higher brain function is in one way or another linked to mobility and that interaction with the world and movement are inseparable. The world needs to be physically approached and probed for cognition and affective behavior to happen. Action always precedes cognition. Embodiment is thereby not a static *a priori* but a continuous process, which plastically shapes the mind through navigation of the world. In that sense, physical activity is a proxy for body and mind in motion and exercise is effective as lifestyle factor not only because of non-specific invigorating systemic effects but also because it re-establishes a natural, fundamental dynamic connection between body, brain and mind.

Problems arise, if this relationship is lastingly severed. In the context of preventive practice for healthy cognitive aging, the idea is that cognition suffers, the reserve formation shrinks and resilience is reduced, if the brain is deprived from opportunities for active engagement through physical interaction and the resulting sensory feedback from the body and the exterior senses. Conversely, therefore, engaging in physical activity is probably the single most valuable preventive action

that anybody can take to re-establish that body–mind connection. But as the brain is required to initiate and maintain physical activity in the first place, also the associated affective states and the resulting sense of a "quality of life" are essential. They drive and motivate the activity and allow to evaluate and value it. The triad of emotions, cognition and motor activity is the key to behavior. The embodied mind is essentially an "embodied mind in motion" and this idea could become the nucleus to a general neurobiological concept of resilience and prevention.

THE REAL-LIFE COMPLEXITY OF LIFE-STYLE AND LIFE-STYLE BASED INTERVENTIONS

But focusing on motoric activity, even though it is extremely effective, is not enough, also because people differ substantially in how easily they engage in it and maintain a lifestyle with regular exercise.

Systematic categorization of the large number of potentially preventive practices, for which at least a certain level of scientific evidence exists, revealed that they appear in fact partly antagonistic and create suggestive tension fields (Kempermann, 2019b). They also add dimensions that are not covered by the well-supported interventions like physical activity. In sum, these potential factors as a whole, more than the well-researched "usual suspects" (exercise, non-smoking, balanced diet, etc.), affect both body and mind and they reflect receiving input as well as generating output. Together are reflecting the embodied mind in its active interaction with the world.

Given that—outside experimental situations—many of these describable subfactors will act in concert, the focus on large effect sizes only might be thus misleading. Both the highly polygenic inheritance and complex individual environmental trajectories (shared and non-shared) will influence the overall outcome. Lifestyle is ultimately a non-linear, non-additive concept and the most successful preventive lifestyle profiles will be highly polyfactorial and multimodal. Presumably they must keep some balance along the seemingly orthogonal trajectories of the matrix. They are intrinsically interactive, which is also reflected in the very large communalities that the known factors (especially physical activity) exhibit in the large epidemiological studies (Norton et al., 2014). For most of the activities, however, such overlap and shared influence has not yet been calculated. It thus seems that we need much more complete models of lifestyle. And at the same time we must learn to understand the relationship between the key dimensions of lifestyle. The resulting reductionism would be considerably different from the one practiced now.

WELLBEING AS CENTER OF LIFE-STYLE INTERVENTIONS

Complex organisms achieve and maintain their bodily equilibria through autonomous systems as well as through willful actions. Emotions signal the diversion from the equilibria and initiate activities. Long-term quality of life and wellbeing are ciphers for the experience of homeostatic states. The emotional connotations are arguably stronger drivers of lifestyle than reason. Unhealthy behaviors result from conflicting emotions and motivations in such situations.

Incidentally, the perceived value of a balance between physical factors on one side and mental, spiritual or social factors on the other and between acts of receiving and of giving is also central and essential to Western and Eastern wisdom traditions on how to lead a good life. These are centered around strong emotional cores.

Invariably these traditions tend to particularly emphasize the spiritual domain but they often involve physical practices and often nutritional guidance as well. Importantly, however, they offer more than regimes of activities. They address the entire human being and they all have an immaterial, spiritual center, transcending the physical world. While they are thus often perceived as in conflict with a scientific world view, they in fact identify central questions of the human condition and are immediately relevant to the lives of millions. Given their presence and influence, it is hard to argue, why they should not be the subject of scientific investigation in a context, which so clearly calls for their inclusion. Such perception might also change, as, for example, the neuroscience of mindfulness and meditation, previously prime examples of such elusive, soft activities has become generally accepted and has led to tangible results.

At the same time, however, many clinical studies in other contexts (especially in oncology) use quality of life measures, assessed by standardized scales and questionnaires as end-point (Soni and Cella, 2002), recognizing that where the patients stand emotionally and how they feel, might often be more relevant than objective clinical endpoints, biomarkers, scores, signs and symptoms alone. In fact, a "benefit" visible in physical parameters or biomarkers but nevertheless associated with prolonged suffering is widely rejected as irrelevant.

Consequently, palliative therapy for fatal disease at the end of life orients itself almost solely on quality of life measures. It has been argued that for old and oldest age, also in the absence of palliative conditions, quality of life should be the decisive variable to guide all medical decisions. It thus is worth further discussion, whether prospectively, in a preventive context and at much younger age, which under the current demographic trends will likely lead to very old age and a great likelihood of multimorbidity—this same variable should not receive even more appreciation and attention.

Quality of life and wellbeing certainly cannot be the sole target of holistic interventions to promote a beneficial, healthy lifestyle, as it is obvious that on a short-term many irrational, unhealthy and potentially damaging behaviors and habits might produce an instantaneous increase in quality of life. But these short-term hedonistic qualities must always be seen in their life-course context. There are in fact different relevant forms of wellbeing coexisting within the same life. This idea again alludes to the religious and wisdom traditions, which tend to distinguish "worldly" short-term bliss from a greater good. That insight, however, is neither religious *per se*, nor does it

necessarily comprise elements of transcendence. But religion is one possible answer to this central question and not surprisingly, thus, religious beliefs and practice have also been found to be associated with health benefits and successful cognitive aging (Peteet and Balboni, 2013; Hosseini et al., 2019; Khalsa and Newberg, 2021). Wellbeing as opposed to momentary bliss is usually associated with states of balance. Healthy lifestyles must achieve such balance in order to become sustainable. Scientifically, this means that understanding the nature, origins and mechanisms of homeostatic states are central to understanding, how we can lead our lives in order to remain prepared for oldest age.

A Research Topic in Frontiers in Aging Neuroscience explicitly assembled reports on studies on "Interventions to Promote Wellbeing in Old Age," presenting numerous interventions, from physical (the large majority) to cognitive and spiritual. A comprehensive editorial outlined the conceptual framework spanned out by this range of interventions. What remained less clear, however, is how all (or many) of the activities might actually integrate to manifest as wellbeing and how wellbeing in turn might act back upon endpoints like cognition, general fitness, etc. (Foster et al., 2019).

BENEFICIAL LIFESTYLES HAVE SOCIETAL NOT ONLY INDIVIDUAL DIMENSIONS

Beneficial interventions that, on the contrary, decrease subjective quality of life face a difficult uphill battle. Health behaviors that are solely relying on reason but acutely evoke negative emotions have poor chances of becoming stable. This applies to exercise regimens, diet recommendations, educational objectives and others. Many standard recommendations for healthy cognitive aging rely on the unrealistic prerequisite that they must be embraced emotionally and become naturally integrated into the quality of life. How this is going to happen is usually left to chance and depends on genetic predispositions, personality traits, past experience and circumstances.

On the other hand, some promising developments might guide the way. The continuing decreases in the risk to develop dementia in consecutive age cohorts (roughly 16% per decade), as detected in the Framingham study, the Rotterdam study and others, have been credited to environmental and lifestyle changes over the past decades that were part of general turns in societal perception and often reflected overarching political decisions (e.g., regarding pollution, smoking ban, etc.; Wolters et al., 2020). They were not, however, the consequences of collective decisions to adopt beneficial lifestyles according to evidence-based check lists with delayed gratification. Socially and environmentally induced behavioral changes can become common sense and greatly matter.

Studies on centenarians and the so-called "blue zones"—regions of the world with an unusually high number of healthy very old people—also revealed that, besides the contribution of the local gene pool, the positive effects on lifespan and health in old and oldest age were usually not due to intentional individual changes in lifestyle but associated with an established way of life, deeply rooted in the society and a shared sets of values. While many attempts have been made to mechanistically deconstruct the blue zones and the lifestyle trajectories of centenarians (again besides deciphering potential genetic bases), the studies rather unanimously point to the existence of a pre-existing mindset that is not focused to achieving old age or health but profoundly anchored in the presence. The subjectively high quality of life reported by many of these oldest-old people is also associated with often rather modest economic means and a high resilience to adverse life events, including war. For them, becoming old in cognitive health is the often (but not even always) welcome side effect of a life at peace with themselves. While it is scientifically challenging to capture this aspect and enter its measure into a comprehensive model of resilience, the reports support the notion that variables other than the objective physical parameters matter and that populations that (besides genetic predispositions) have achieved collective life styles that support healthy cognitive aging and longevity do so implicitly and without perceived hardship on a path toward a distant goal.

Together these insights indicate that, besides providing supportive legal and political frameworks, the role of society in forming and sustaining lifestyle goes much deeper.

While it will not be realistic to actively emulate the complexity of blue zones and to call for societal change as a feasible first step, the most important aspect to learn from these environments is the holistic nature of the life-style they represent, centering around a subjective quality of life and peace of mind. The problem, of course, is that exactly these variables are latent and evade reductionistic experimental approaches. But as little as polygenic effects can be pieced together bottom-up from series of pseudo-mendelian experiments on individual genes, lifestyle is much more than the sum of quantifiable measures but has emergent qualities.

A reasonable first step toward comprehensive preventive measures that relate to lifestyle in a deeper sense and to the embodied mind in motion is therefore to explore known activities that are partly reductionistic in that they are still identifiable "interventions," rather than as complex as life itself, but are experienced as holistic and increasing wellbeing now and not only benefits later.

EXAMPLES OF BODY–MIND LIFE-STYLE ACTIVITIES LEAD THE WAY

Hiking

Hiking is the combination of physical activity with experience of nature, either in deliberate solitude or as social activity. Intensity levels are low to medium at most times, but endurance can be a major factor, when hikes become long and the terrain challenging. Important physiological characteristic of hiking is the regular pace and sensory richness, including proprioceptive input on varying undergrounds. A meta-analysis of 26 studies on long-distance hiking revealed a positive association with mental health,

most notably stress reduction, but less clear for general wellbeing (Mau et al., 2021).

Given the popular attention that hiking receives as potential health behavior, the number of actual studies is, however, surprisingly low. That hiking exposes to an experience of nature is considered a central element [see the extensive narrative review by Mitten (2009)]. Another aspect that is considered essential is the room the that long-distance hiking provides for personal reflection (Mau et al., 2021).

Long-distance hikers were studied in a questionnaire study (Mayer and Lukács, 2021). The authors summarize the findings as: "Hikers had mainly intrinsic motivations to complete long distances including overcoming new challenges, finding the physical boundaries, experiencing a state outside the comfort zone, belonging to a special group with similar interest and attracted by the beauty of nature. Overcoming all these embodied in a flow experience that took them further to perform the new long-distance trails."

There is an overlap between the experience and effect of hiking with long-distance running, but for runners, the sportive aspect usually dominates. Nevertheless, many long-distance runners also emphasize the meditative qualities of long runs ("flow") and for many running in the outdoors stands for a primal interaction between the body and nature. Flow is characterized as state of enjoyment and reduced self-awareness that occurs during an optimal task performance with low demands to attention. There are still relatively few studies on the physiology of the "flow" state but it appears to be a central moment in explaining the perceived or real neural effects of these activities, deserving further attention.

An impressive 2021 retrospective study on 200,000 participants of Sweden's long-distance cross-country ski race Vasalopet, who were followed for up to 21 years, revealed a strong association of physical activity with a reduced risk to develop anxiety. Participation in the popular race has been taken as indication of general physical activity, as the race requires extensive preparation. But cross-country skiing is also a classical outdoor activity, and people in the North engage in it especially during the dark period of the year. The authors write: "We identify a need for future studies to gain deeper knowledge about the impact of these confounding psychological factors, taking both environmental, genetic, and epigenetic background into account." What appears to be a confound from the perspective of studying abstract physical fitness, might actually represent a very interesting contributing factor by itself (Svensson et al., 2021).

The assumed role of the "green outdoors" on the brain has been addressed in a study with unprecedented depth. In longitudinal series of multiple MRT scans over 6–8 months, Kühn et al. (2021) found that the time spent outdoors was positively associated with gray matter volumes in the right prefrontal cortex and self-reported positive affect (after controlling for numerous parameters, including "hours of sunshine").

Hiking (or walking) appears as the least complex example of a body–mind activity with beneficial effects on the brain including increasing resilience (Tomata et al., 2019).

Playing a Musical Instrument

Playing the musical instrument might be the best-known and best-studied holistic intervention to date. A relatively strong case can be made for a wide range of positive effects of music on the brain. Playing a musical instrument is an activity that combines various aspects of activity, from motoric to cognitive, often including social interaction. The position of music in the evolutionary perspective is enigmatic. Music, being clearly an achievement of civilization must root on primordial functions and structures that evolved with the brain. This implies that besides all positive aspects of music itself, music is always also a representation of a more general principle. The embodied mind in motion might be a coarse yet fitting description of this condition. Unlike in the example of hiking, musicians are exposed to the experience of a world of its own, produced by the mind, alone or with others, and related to a skillful motor activity in the world. Music is at the same time a language directly speaking to the emotional brain and to the intellect and has a strong social component. There is also anecdotal evidence of particular longevity among (classical) musicians, especially conductors.

Again, relative to the public attention that playing an instrument attracts as a putative approach to prevention of dementia, the number of actual studies is slim. A meta-analysis over three studies of high quality described an impressive 59% reduction in the risk of developing dementia, but cautioned that the size of the evidence base is limited, the studies cover low numbers of participants and causality cannot be established (Walsh et al., 2021). Self-reported musical activity has also notable socio-economic covariables. Nevertheless, a cohort study which assessed the effect of the frequency of playing music in mid-life on later-life cognition revealed that the most active musicians had 80% greater odds of being in the top cognitive decile (Walsh et al., 2021).

Singing will be the most essential form of "playing an instrument," requiring nothing but the body and breath as means to physically produce music. The relationship between body and mind is rather obvious here. Singing in a choir, which also involves social aspects, consequently has expected effects on quality of life (Johnson et al., 2013). Another study found no effects on cognition (Pentikäinen et al., 2021). Reported subjective benefits, however, were extremely positive in the largest survey to date (Moss et al., 2018), suggesting that the individual interaction effect of objective and subjective variables needs to receive more attention.

Dancing

Regarding the beneficial effects of dancing on successful cognitive aging, reference is usually made to the impactful report by Verghese et al. (2003), which was a prospective observational study of self-reported leisure activities. To date, there is an overall relatively large literature on the positive effects of dancing on cognition. Meta-analyses of the available literature support positive effects of dance interventions, for example on global measures of cognition, on executive functions and on memory performance (Meng et al., 2020).

When Karkou and Meekums (2017), however, attempted a systematic review for the Cochrane data base of dance therapy for dementia, they did not find studies that could be included into their analysis, because none was conducted by a certified dance movement therapy practitioner. This criterion might be counterproductive for a general evaluation of dance as effective intervention and contradicts the idea of employing activities that people can pursue on their own and integrate into their daily lives. A less restrictive review of essentially the same literature provided support of the idea that dancing therapy would have positive efficacy for cognitive, physical, emotional and social performance in dementia, but also cautioned that the overall quality and rigor of the studies was questionable (Klimova et al., 2017). A case study with a streamed dance course delivered to participants in care homes concretely addressed the aspects of embodiment and highlighted effects on creativity and social inclusion rather than classical endpoints such as "cognitive performance" (Kontos et al., 2021).

This range of statements showcases the problematic evidence situation for dancing as lifestyle intervention for therapy or secondary prevention. It also underscores that the vast majority of available studies does not prominently take on a body–mind perspective, appreciating dancing as a holistic, embodied activity with preventive (side-) effects but rather as a conventional physical intervention.

Accordingly, the frequently found statements that more research would be needed to address the question, whether dancing can lead to more cognitive benefits than other types of physical activity and exercise (Hewston et al., 2021), is understandable from a reductionistic point of view but misses the central question of wellbeing as driver and result as well as a holistic approach to the highly multi-modal and complex intervention "dance."

In the reported studies, dancing usually is ballroom dancing, folk dancing or explicitly therapeutic forms of dance, but rarely the more professional versions of ballet and modern dance (Karpati et al., 2015).

Yoga

Yoga differs from the other mentioned activities in that it explicitly addresses both body and mind. Its primary objective is related to the self of the person engaging with the activity, not to nature, music, or social interactions, etc., rendering it more introspective. For many, Yoga and similar activities are attractive because of their immediate effects on bodily and spiritual wellbeing, not because of a delayed health effect or through competition, as in other sports. There are diverse Yoga styles, of which the most relevant in the context or prevention and resilience probably are combinations of dynamically flowing series of poses with elements of meditation, linked by a focused awareness of breathing. Because of the great number of styles and lacking standards for research, the body of scientific literature on Yoga, while being vast, remains inconclusive. Nevertheless, it is the only activity, for which the body–mind aspect has been explicit subject of the research, and as problematic as the overall level of evidence still might be, there is also no doubt that practicing Yoga (as well Tai Chi, etc.) can have numerous positive effects on cognition, also in older adults (Wu et al., 2019). The growing interest in Yoga and its health effects, however, is currently leading to an increasing number of studies with greater quality. It remains to be hoped that on the longer run they do not attempt to view the holistic intervention through the lens of the classical reductionistic single-intervention approaches but develop novel formats that also incorporate embodiment as an essential neurobiological principle and embrace the complexity of the intervention.

As there is already an increasingly solid evidence on structural and functional effects of Yoga on the brain (Gothe et al., 2019), including some first results on cellular aging (Tolahunase et al., 2017).

The point is not, whether any component of Yoga might by itself and stripped from the other components might already have similar effects as Yoga as a whole, but that Yoga has emerging benefits that surpass the addition of identifiable components. Improved wellbeing now and in the future plus health benefits will be more important than health benefits alone, even if the latter were larger in a different context. Wellbeing matters.

THE NEUROBIOLOGY OF EMBODIED PREVENTION

For a deeper understanding of complex life-style "interventions" that address body and mind, two complementary approaches must be taken. The first is to improve studies in humans engaging in the actual activity, the second to better understand the underlying fundamental biological principles. These must be seen together and the resulting research must be highly interdisciplinary in scope (**Figure 1**).

The examples of hiking, yoga, etc. show that such studies are very challenging, if the analysis should go beyond the reductionistic approach as taken for identifiable single factors and reach the emergent qualities of the intervention. The additive method of conventional multi-modal trials [such as FINGERS (Ngandu et al., 2015)] is ultimately not sufficient, because the holistic interventions cannot be easily deconstructed into factors without damaging the critical interaction effects and by ignoring present wellbeing as driving force of success. Mechanistically, the bottom-up approach is bound to fail in much the same way as it is impossible to understand complex polygenic traits from the analysis of single associated genes (Boyle et al., 2017). A first meta-analysis of multidomain interventions did not yield evidence of clear benefits (Hafdi et al., 2021).

Whereas the existing large-scale trials still support the notion of an additive and complementary effect in multimodal interventions, most concrete prospective intervention studies on hiking, dancing, yoga, etc. have as yet yielded limited evidence on the applied objective scales, even though, qualitatively, participants described substantial subjective benefits. These highlight the limits of standardization and underscore the individuality (and subjectivity) of the response in life-style interventions. The impact of this subjectivity gap for basic research has as yet received little attention. This is no wonder,

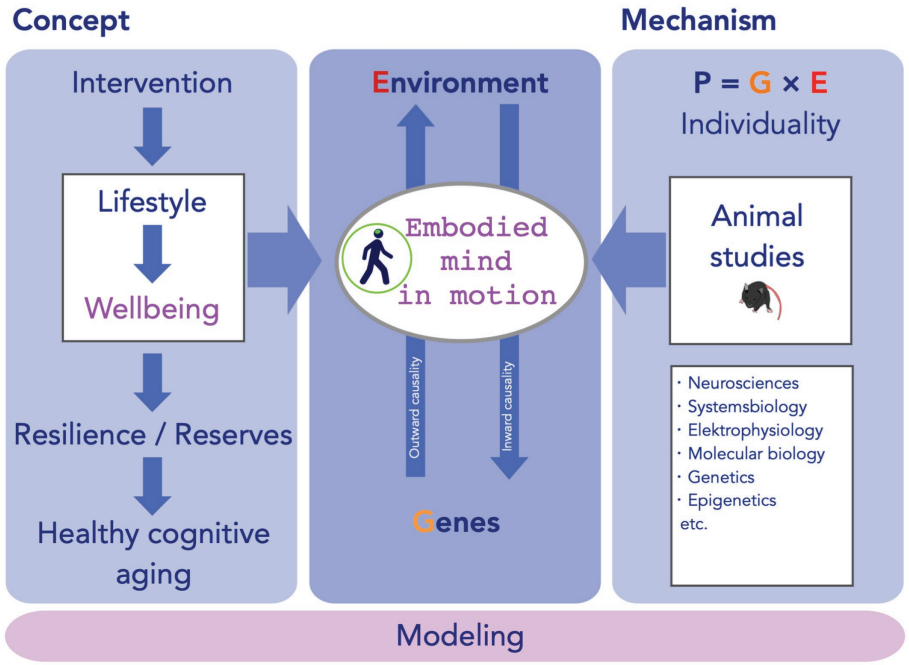

FIGURE 1 | Embodied prevention. The concept underlying lifestyle interventions for healthy cognitive aging is based on the assumption that a lifestyle-changing intervention results in an increase in resilience in old age and a preservation of reserves. The emphasis here lies in the fact that in order to be sustainable, lifestyle must also have motivating effects on wellbeing now. The embodied mind lies at the center of this context, because body and mind cannot be thought separately in this context. Behavior in the environment and the underlying genetic predispositions and causes are linked in a bi-directionality chain or network of causalities, intersecting in the embodied mind in motion. Animal studies and other types of reductionist research can aid understanding this core concept and unraveling mechanisms underlying the equilibria of wellbeing, the embodiment in motion itself, and the interindividual variation of this effect, by building upon the fundamental principle that any phenotype and its variation draws from an interaction of genetic and non-genetic causes. Here the non-shared factor of the environmental effect, which includes individual behavior and actions is of particular interest. Future models of lifestyle based embodied prevention need to include all three pillars.

given that many essential concepts like subjectivity and wellbeing cannot readily be approached and measured in reductionistic settings. The same applies to the activities themselves: hiking, playing a musical instrument, dance and yoga cannot be studied in laboratory animals.

While this is true, basic neurobiological research, especially with a systems biology perspective, can nevertheless critically help addressing these questions, because the biological perspective zooms in on the evolutionarily conserved fundamental mechanisms that underlie the adaptability to the challenges of long life in a dynamic complex world. The depth of phenotyping under controlled conditions, the possibility to control or manipulate genetics and the environment, and longitudinal tracking and monitoring offers unique opportunity to study the embodied mind in motion under reductionistic conditions, even though the elements of subjectivity and quality of life largely have to be left out. Embodiment is, after all, a profoundly biological concept, even though it was developed in other contexts. In addition, embodiment is part of exciting new concepts in neurorehabilitation based on virtual reality to target declining spatial memory and navigation (Tuena et al., 2021).

In basic neurobiological research, the vast animal literature on "enriched environments" is concerned with the concept that exposure to environments that induce behavioral activity and learning, fundamentally shape the brain, its connectivity and its functions (van Praag et al., 2000; Nithianantharajah and Hannan, 2006; Kempermann, 2019a). Although the paradigm has not yet been explicitly brought into connection with the idea of embodiment, it actually captures the processual aspect of embodiment by highlighting the dynamic link between form and function, called plasticity. Behavioral activity matters for brain integrity and function and this interaction is reciprocal.

A neurobiological perspective on "lifestyle" introduces a new and different reductionism to the study of lifestyle. This reductionism embraces data-driven and systems biology approaches to take head-on the complexity of holistic lifestyle interventions and activity-based resilience by using, for example, model organisms.

Any phenotype—and successful cognitive aging is an observable trait and thus biologically speaking a phenotype—is determined by the interaction of genetic and environmental factors. This interaction can be explored in animal studies by targeted manipulations that are impossible in humans.

Both the risk of and the resilience against neurodegenerative disease and impaired cognitive aging are complex quantitative traits with massively polygenic inheritance but also a strong non-genetic component—hence the impact of lifestyle. What we perceive as specifically human components, e.g., subjective experience and wellbeing, are to a large extent part of the environmental factor. The nature of the interaction effects,

however, can be explored with surrogate parameters, assumed homologs of "life-style" in animals.

The term "environment" is a complex construct that goes beyond the physical outer environment. That component, the non-shared environment, includes the ways we interact with the world, transform and shape it, our social interactions, all behaviors of the individual and of others, and many other identifiable aspects that together build the variable individual response to a challenge.

In a highly reductionistic study in mice, it was possible to isolate the impact of the so-called "non-shared environment," that is the component of the environmental factor to phenotypic variation that consists of the individual behavior even in an environment that is shared and—which is possible in these studies—if the genetic background is kept constant (Freund et al., 2013). That study revealed that individual activity in fact matters, even though in naturalistic settings and especially in humans, the situation must inevitably be more complex and the effect sizes will vary. The effects are also dependent on the individually variable impact of the genetic and the shared non-genetic component on the activity. Irrespective of this, some key concepts of that study (the relationship between exploratory behavior or territorial coverage and brain plasticity) has already been translated to a human study (Heller et al., 2020).

The inward (from behavior to genes) and outward (from genes to behavior) pointing chains or networks of causalities are interdependent (Kempermann, 2019a). The level of cells, tissues and systems is a tangible place where the effect of the reciprocal interaction of these intersecting chains of causality are concentrated and thus can be studied. This, together with the superior role of motor functions (as discussed above), establishes a neurobiological construct of embodiment that emphasizes dynamical change.

In addition, the idea of embodiment has more recently also been explicitly extended to include cellular processes, including "cellular memory," immunity, the microbiome, etc., arguing that aspects of what we used to consider brain functions are in fact distributed to the body and thus inseparable from it (Verny, 2021).

Ultimately, below all this lie evolutionary questions. Like anything else in biology, also lifestyle-based resilience and the hypothesis of the "embodied mind in motion" will make sense only in the light of evolution. Lifestyle is not only a social construct and a fashionable label for individual actions, but also a possibly ill-chosen term for a fundamental principle of life that deserves neurobiological attention.

CONCLUSION

The proposed framework of the "embodied mind in motion" intends to improve the limitations of a common perspective on the life-style based promotion of healthy cognitive aging by shifting the focus from external (single interventions with large effect size) to internal (wellbeing as mediating endophenotype). By emphasizing communality between known factors, their partly antagonistic nature and the potential impact of a large number of factors with small effect size the concept allows for accommodating large inter-individual variability and the underlying real-life complexity in preconditions, personal biographies, and varying circumstances. By rooting in an evolutionarily conserved key relationship between movement and cognition the increase in complexity (by moving from few factors to all factors) becomes approachable in reductionistic experiments, including in animal studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Sense of Coherence Mediates the Relationship Between Cognitive Reserve and Cognition in Middle-Aged Adults

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In recent years, supported by new scientific evidence, the conceptualization of cognitive reserve (CR) has been progressively enriched and now encompasses not only cognitive stimulating activities or educational level, but also lifestyle activities, such as leisure physical activity and socialization. In this context, there is increasing interest in understanding the role of psychological factors in brain health and cognitive functioning. In a previous study, we have found that these factors mediated the relationship between CR and self-reported cognitive functioning. In this study, we have confirmed an association between two important constructs included in the psychological wellbeing and salutogenic models, "purpose in life" and "sense of coherence," CR, as assessed using a questionnaire, and cognitive functioning, as evaluated using a comprehensive neuropsychological battery. Results from 888 middle-aged healthy participants from the Barcelona Brain Health Initiative indicate that both sense of coherence (SoC) and CR were positively associated with verbal memory, reasoning and attention, working memory, and global cognition. Moreover, the relation between CR and cognitive functioning in the different domains is partially mediated by SoC. When we controlled for brain integrity, introducing into the model neurofilament light chain measures, the mediator role of SoC was confirmed for reasoning and attention and global cognition. However, purpose in life was not associated with cognitive functioning. These results reveal the central role of the SoC construct, which mediates the association between classic CR estimates and cognitive functions, potentially representing a modifiable target for interventions that aim to promote brain health.

Keywords: sense of coherence, purpose in life, cognition, cognitive reserve, brain health

INTRODUCTION

Recent biomedical research is increasingly focused on understanding why a substantial portion of individuals remain cognitively and functionally normal throughout their lifetime, irrespective of the occurrence of age-related brain changes or the presence of brain pathology (Arenaza-Urquijo and Vemuri, 2018). Parallel to experimental evidence that a large number of factors, both modifiable and non-modifiable, play a role and interact in determining different brain and behavioral trajectories during the lifespan (Di Marco et al., 2014; Livingston et al., 2020), classical theoretical models, such as cognitive reserve (CR), are constantly evolving and expanding.

Among the different CR conceptualizations proposed in the past few decades, we considered a dynamic model of reserve that includes those experiences that explain how successfully a person can cope with age, disease-related brain changes, or achieve better performance on cognitive tasks due to better brain network efficiency (Steffener and Stern, 2012). In this sense, CR is considered as "the ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies" (Stern, 2002). This ability is associated with both early and late-life socio-behavioral experiences pertaining to a broad variety of domains.

Although original conceptualizations of CR mainly considered the roles of education and occupation as proxy variables, in combination with measures of premorbid intelligence estimations (Stern, 2012), a broad variety of activities through life are now being considered (Stern et al., 2020). In this regard, the role of psychological factors, including personality traits, coping strategies, negative thinking, and attitude toward life, has been investigated recently as important factors in promoting brain health and resilience (Franchow et al., 2013; Ryff, 2014; Bartrés-Faz et al., 2018; Arenaza-Urquijo et al., 2020; Colombo et al., 2020; Marchant et al., 2020).

Similarly, different variables included in the psychological wellbeing construct proposed by Ryff (1995) (e.g., Purpose in life, PiL), as well as dimensions included in the salutogenic model of Antonovsky (1993) (sense of coherence, SoC), have been related with higher levels of mental health *via* stress management and self-regulation mechanisms (Durand-Bush et al., 2015; Mc Gee et al., 2018). These eudaimonic dimensions, encompassing the experience of fulfillment achieved through self-actualization and a goal-directed existence, have been consistently considered as protector factors for biological markers related to the stress pathway, such as cortisol levels (i.e., Pressman et al., 2019) and inflammatory markers (i.e., Ironson et al., 2018), and have been shown to interact and moderate the relation between classical proxies of CR and inflammatory processes (see Ryff, 2014 for a review).

Sense of coherence represents the central factor on the salutogenic model, originally proposed by Antonovsky (1990). This construct is defined as a "global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that: (1) the stimuli deriving from one's self internal and external environments in the course of living are structured, predictable, and explicable; (2) the resources are available to one to meet the demands posed by these stimuli; and (3) these demands are challenges, worthy of investment and engagement" (Antonovsky, 1996). Hence, SoC has a cognitive and behavioral-instrumental dimension, being considered the "cognitive" component of the meaning in life theory (Martela and Steger, 2016). This cross-cultural construct represents a general orientation in promoting health by allowing individuals to actively use available internal and environmental resources to cope with adverse events and, ultimately, to boost resilience to them (Antonovsky, 1990).

Epidemiological and clinical studies have shown that SoC is an important health-promoting resource, and it has been related to the quality of life and a broad range of health-related variables, as well as to the prevalence of distinct pathological conditions, including depression, cardiovascular accidents, and mortality (Lundman et al., 2010; Boeckxstaens et al., 2016; Mittelmark et al., 2016; Huang et al., 2017).

Sense of coherence has also been consistently associated with classical proxies of CR, such as education (Giglio et al., 2015) and leisure-time physical activity (Monma et al., 2015), and has been positively associated with both self-reported (Read et al., 2005) and measured cognitive functioning (Boeckxstaens et al., 2016). Interestingly, a longitudinal study in older adults observed a parallel decline in cognition and SoC over time (Lövheim et al., 2013), supporting the role of this construct in cognition and optimal functioning.

Purpose in life, instead, represents a motivational psychological construct relating to the notion of having a sense of future-oriented and meaningful goals in life. It is one of the six factors composing the psychological wellbeing model proposed by Ryff (1995), together with autonomy, personal growth, environmental mastery, positive relationships, and self-acceptance. Higher levels of PiL could moderate the impact of biological risk factors, such as inflammatory markers, and may be associated with a better capacity to face challenging conditions that could affect mental and physical health (see Ryff et al., 2016 for a review). It has been shown that PiL is related to a reduction in the incidence of various health-related conditions, such as stroke, cardiovascular accidents, disability, and other causes of mortality (Kim et al., 2013; Cohen et al., 2016; Kim and Park, 2017). In the context of cognition and dementia, PiL has been associated with better cognitive function in healthy adults, reduced incidence of mild cognitive impairment (MCI) and risk of developing Alzheimer's disease (AD), and crucially with better cognitive functioning in the presence of more AD pathology (Boyle et al., 2010, 2012; Lewis et al., 2016).

The associations between psychological constructs and cognitive outcomes, as well as their consistent relation with classical proxies of CR, suggest their possible role in the relation between CR and cognition. In fact, higher estimates of these constructs could influence classical proxies of reserve (e.g., social aspects), or be influenced by them (e.g., educational level), modifying their relationship with cognitive functioning.

In a previous study (Bartrés-Faz et al., 2018), we already observed that both SoC and PiL mediate the relation between classical proxies of CR and self-perceived cognitive functioning.

In this study, we wanted to make a further step by exploring the relationship between these psychological constructs, CR, and objective cognitive performance. This was assessed through a formal neuropsychological evaluation in a large sample of middle-aged and older adults (1) using objective measures of cognitive functioning and (2) exploring different cognitive domains separately.

In line with the results of our previous study, we hypothesized that SoC, seen as a psychological cognitive construct related to resources control and managing in response to environmental demands, would be particularly associated with general cognitive functioning and executive functions, while PiL may show a weaker association with cognitive measures. To achieve the objectives linked to these hypotheses, we employed a "controlling" model that explores the association between proxies of CR and cognition, and the mediator role of two psychological constructs, in light of similar levels of brain status in healthy middle-aged adults.

MATERIALS AND METHODS

Participants

In the framework of the Barcelona Brain Health Initiative (BBHI) (see Cattaneo et al., 2018, 2020 for details), 888 participants (433 women, mean age = 53.35, standard deviation = 7.1, range = 42–67) that underwent in-person assessments participated in the study. Participants were selected if they accomplished a cognitive assessment and completed an online survey on CR (Rami et al., 2011), SoC, and PiL estimates (Díaz et al., 2006; Virués-Ortega et al., 2007). Furthermore, participants did not present with any neurological or psychiatric diagnosis at the time of entering the study.

Assessment

Neuropsychological Assessment

Neuropsychological testing was administered by two expert neuropsychologists (V.A. and C.P.) in a single session of approximately 90 min (see Cattaneo et al., 2018). Tests were administered in a fixed order: direct and inverse digit span (Peña-Casanova et al., 2012), Trail Making Test Parts A and B (Peña-Casanova et al., 2012), Reasoning Matrix (Weschler, 2008), Rey Auditory-Verbal Learning Test (Bowler, 2013), block design test (Weschler, 2008), letter-number sequencing (Peña-Casanova et al., 2012), digit-symbol substitution test and cancelation subtests from Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Weschler, 2008), and Corsi block-tapping test (Peña-Casanova et al., 2012).

Neurofilament Light Chain Measurement

We collected blood samples using ethylenediaminetetra-acetic acid (EDTA) tubes during the medical assessment of the BBHI, and plasma was aliquoted and stored in a freezer at −80°C in a biobank facility following standard procedures usually employed for clinical purposes. Plasma Neurofilament light chain (NfL) concentration, a general marker of neurodegeneration (Teunissen et al., 2022), was measured using the single-molecule array (Simoa) NF-light Advantage Kit on an HD-X instrument as described by the kit manufacturer (Quanterix, Billerica, MA, United States). The limit of quantification was 2.7 pg/ml, and the limit of detection was 0.3 pg/ml. For the quality control (QC) sample with an 11.2 pg/ml concentration, repeatability was 3.6%, and intermediate precision was 5.0%. For a QC sample with a 115 pg/ml concentration, repeatability was 5.3%, and intermediate precision was 6.8%. The measurements were performed at the Clinical Neurochemistry Laboratory at the University of Gothenburg by board-certified laboratory technicians who were blinded to clinical data.

Online Surveys

Cognitive reserve was estimated using a short questionnaire validated in the Spanish population and previously used in studies with healthy elders and patients with AD (Rami et al., 2011). The questionnaire obtained information about six main proxies of CR entailing attained level of education, occupation, musical formation, language skills, reading activity, and intellectual games. The total score (from 0 to 25) was obtained by directly adding the single response scores. Higher scores in this questionnaire correspond to higher levels of CR (refer to **Table 1**).

Sense of coherence was evaluated using the Spanish version of the orientation to life questionnaire (OLQ-13; Lizarbe-Chocarro et al., 2016). This 13-item scale represented an abbreviated version of the original 29-items tool and uses a 7-point Likert-type response scale (range: 0–91). Higher scores in this scale correspond to higher levels of SoC (refer to **Table 1**).

Purpose in life was measured using the PiL subscale of the Spanish version of Ryff's wellbeing scale (van dierendonck et al., 2008) that with a Likert-type scale ranging from 1 (strongly disagree) to 6 (strongly agree), whereby higher scores correspond to higher levels of PiL (refer to **Table 1**).

Statistical Analysis

First, as performed in previous studies of our group (e.g., España-Irla et al., 2021), we transformed raw scores obtained by cognitive tests to *z*-scores, then, to create composite scores of different cognitive domains, we ran an exploratory principal component analysis using Oblimin rotation and fixed the acceptable level of factor loading to 0.30 (Hair et al., 1998). Second, we explored the association between SoC and PiL by running Spearman correlations.

Finally, we ran two multivariate linear regression models, one for SoC and another for PiL, to control for collinearity due to the high correlation between these two measures, using the different composite cognitive scores (see below) as dependent variables and CR, age, gender, and the psychological construct

TABLE 1 | Results of online surveys.

Survey	Mean (SD)
Cognitive reserve (CR)	19.76 (3.62)
Sense of coherence (SOC)	66.92 (12.09)
Purpose in life (PiL)	28.73 (6.05)

estimation as regressors. Based on the results obtained, when possible, mediation analyses were undertaken using the Preacher and Hayes' mediation procedure (Preacher and Hayes, 2008). Models were repeated in a subsample ($N = 756$) where NfL data were available. Here, NfL was used as a covariate in the analyses to adjust for neurodegeneration.

All statistical analyses were carried out using the SPSS version 23.0 software (Statistical Package for Social Sciences, Chicago, IL, United States), and mediation analyses were carried out using the PROCESS macro for SPSS (Preacher and Hayes, 2008).

RESULTS

Cognitive Composite Score Calculation

Neuropsychological raw data of the 888 participants (refer to **Table 2**) were transformed into *z*-scores and used in the principal component analysis. Bartlett's test revealed a significant relationship between the factors ($p < 0.001$), and the Kaiser-Meyer-Olkin (KMO) test confirmed that the data were suitable for factor analysis (KMO = 0.63).

The principal component analysis resulted in four components, the first included all measures of the Rey Auditory Verbal Learning Test (immediate recall = 0.88, delayed recall = 0.91, and recognition = 0.79), indicating a verbal memory domain. A second reasoning and attentional component comprised the Trail Making Test A (0.77), the block design test (0.74), the digit-symbol substitution test (0.70), the WAIS-IV matrix reasoning (0.65), and the cancelation test (0.53). The third factor reflecting working memory contained digit span backward (0.79), digit span forward (0.78), and the letter-number sequencing tests (0.70). Finally, set-shifting abilities were reflected in a fourth component, with the Trail Making Test Part B (0.97) and the Trail Making Test Part B-A (0.97). Based on the factorial structure obtained, we calculated composite scores of the four domains as the mean of *z*-scores of each neuropsychological test. Moreover, we calculated a global cognition composite as the mean of all the transformed *z*-scores.

TABLE 2 | Results of formal neuropsychological testing of participants.

Neuropsychological test	Mean (SD)
Digit span forward	6.14 (1.21)
Digit span dackward	4.92 (1.10)
Letter-number sequencing	5.74 (1.04)
RAVLT immediate recall	51.84 (8.65)
RAVLT delayed recall	11.31 (2.68)
RAVLT recognizing	14.35 (1.20)
WAIS-IV logical matrices	19.97 (3.39)
WAIS-IV block design	46.10 (10.44)
Digit symbol substitution test	77.90 (13.41)
WAIS-IV Cancelation	41.72 (8.38)
TMT A	27.51 (8.69)
TMT B	79.14 (26.34)
TMT B-A	51.60 (24.64)

Sense of Coherence and Purpose in Life

Spearman correlations revealed a very strong positive association between SoC and PiL ($\rho = 0.68$, $p < 0.001$).

Sense of Coherence, Cognitive Reserve, and Cognition

Verbal Memory

The multivariate regression model results were statistically significant ($F = 45.91$, $p < 0.001$) and explained 21% of the variance.

Analyses revealed that memory was associated with age ($F = 78.071$, $p < 0.001$), gender ($F = 63.851$, $p < 0.001$), CR ($F = 61.990$, $p < 0.001$), and SoC ($F = 5.110$, $p = 0.024$). In addition, bootstrapped mediation analysis revealed that SoC significantly and partially mediated the association between CR and cognitive functioning in this domain (5,000 bootstrap samples, 95% CI 0.002–0.020; see **Figure 1**). The model explained 19% of the variance without mediators and 20% when SoC was included as a mediator.

Reasoning and Attention

In this case, the multivariate regression model results were statistically significant ($F = 69.50$, $p < 0.001$) and explained 28% of the variance.

Reasoning and attention were associated with age ($F = 259.722$, $p < 0.001$), CR ($F = 82.867$, $p < 0.001$), and SoC ($F = 4.258$, $p = 0.039$). Also, in this case, mediation analysis indicated that SoC significantly and partially mediated the association between CR and cognitive performance (5,000 bootstrap samples, 95% CI 0.002–0.024; see **Figure 2**). The model

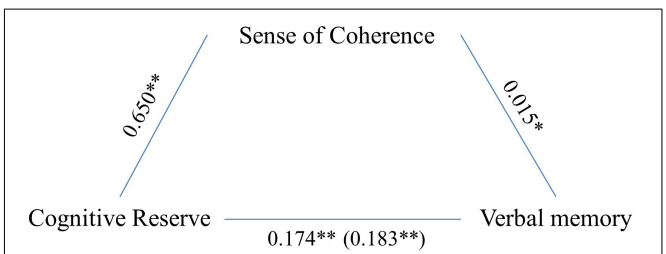

FIGURE 1 | Sense of coherence (SoC) as a partial mediator of the association between CR and verbal memory. Values are *B* coefficients (*$p < 0.05$; **$p < 0.01$); values within parentheses represent total relationship.

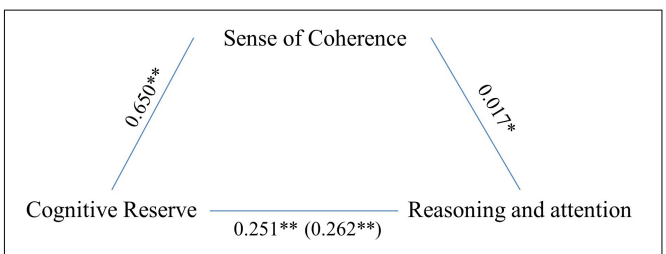

FIGURE 2 | Sense of coherence as mediators of the association between CR and reasoning. Values are *B* coefficients (*$p < 0.05$; **$p < 0.01$); values within parentheses represent total relationship.

explained 27% of the variance without mediators and 28% when SoC was introduced as a mediator.

Working Memory

Multivariate regression model results were statistically significant ($F = 15.43$, $p < 0.001$) but explained only 8% of the variance.

However, working memory results were associated with age ($F = 12.571$, $p < 0.001$), gender ($F = 11.752$, $p < 0.001$), CR ($F = 44.183$, $p < 0.001$), and SoC ($F = 4.439$, $p = 0.035$). Further mediation analysis indicated that SoC significantly and partially mediated the association between CR and cognitive functioning in this domain (5,000 bootstrap samples, 95% CI 0.001–0.018; see **Figure 3**). The model explained 7% of the variance without mediators and rose to 8% when SoC was included as the mediator.

Set Shifting

The whole regression model results were statistically significant ($F = 35.83$, $p < 0.001$) and explained 16% of the variance.

Set shifting results were only associated with age ($F = 121.658$, $p < 0.001$) and CR ($F = 53.326$, $p < 0.001$) but not with SoC ($F = 0.001$, $p = 0.973$).

Global Cognition

For global cognition, the multivariate model results were statistically significant ($F = 83.40$, $p < 0.001$) and explained 32% of the variance.

Global cognition results were associated with age ($F = 78.071$, $p < 0.001$), CR ($F = 144.702$, $p < 0.001$), and SoC ($F = 6.995$, $p = 0.008$). Again, mediation analysis indicated that SoC significantly and partially mediated the association between CR and cognitive performance (5,000 bootstrap samples, 95% CI 0.009–0.056; see **Figure 4**). The model explained 31% of the variance without mediators and 32% with SoC as a mediator.

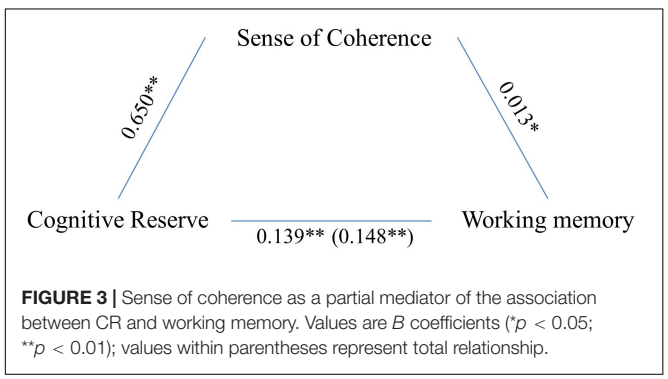

FIGURE 3 | Sense of coherence as a partial mediator of the association between CR and working memory. Values are *B* coefficients (*$p < 0.05$; **$p < 0.01$); values within parentheses represent total relationship.

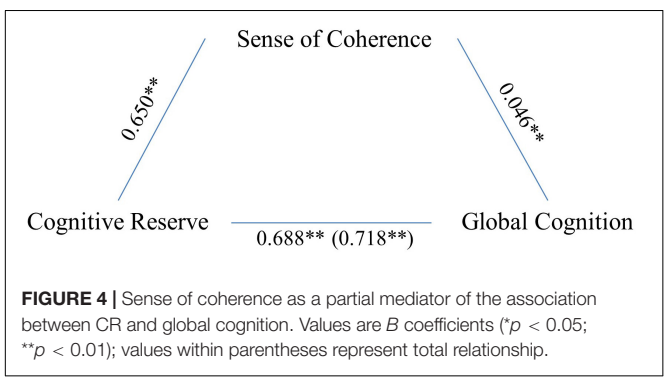

FIGURE 4 | Sense of coherence as a partial mediator of the association between CR and global cognition. Values are *B* coefficients (*$p < 0.05$; **$p < 0.01$); values within parentheses represent total relationship.

Neurofilament Light Chain

We repeated the previous analysis in a subsample ($N = 756$), introducing NfL as a covariate to confirm our results that SoC exerted a modulation effect, while accounting for a measure reflecting brain status, as recommended in the operational definitions of CR by Stern and collaborators (Stern et al., 2020). CR was significantly associated with all cognitive domains, while SoC was associated with reasoning and attention ($F = 4.328$, $p = 0.038$) and global cognition ($F = 5.317$, $p = 0.021$) and only partially associated with episodic memory ($F = 3.045$, $p = 0.081$) and working memory ($F = 2.862$, $p = 0.091$). When we ran mediation models for significantly associated domains, we found that SoC partially mediated the relationship between CR and reasoning and attention (5,000 bootstrap samples, 95% CI 0.002–0.028) and global cognition (5,000 bootstrap samples, 95% CI 0.007–0.061).

Purpose in Life, Cognitive Reserve, and Cognition

Multivariate analysis revealed that PiL was not significantly associated with verbal memory ($F = 0.326$, $p = 0.568$), reasoning and attention ($F = 0.851$, $p = 0.356$), working memory ($F = 0.037$, $p = 0.847$), cognitive flexibility ($F = 1.373$, $p = 0.242$), or global cognition ($F = 0.003$, $p = 0.957$). Results were confirmed when we introduced NfL in the model as a covariate.

DISCUSSION

In this study, we explored the relationship between two psychological constructs (SoC and PiL), CR, and cognition for different cognitive domains. We used a "controlling" model that explores the association between proxies of CR and cognition and the mediator role of two psychological constructs, in light of similar levels of brain status (Stern et al., 2020). In a first analysis, similar brain status was assumed considering the characteristics of our healthy middle-aged participants, while in a second analysis realized in a subsample, we adjusted for a neurodegeneration marker, namely NfL, to confirm the obtained results.

Present findings indicated that CR was associated with all cognitive domains, while SoC was related to composite scores in verbal memory, reasoning and attention, working memory, and global cognition. Moreover, SoC exerted a mediator role on the relationship between CR and all these cognitive measures. When we corrected for a measure of brain status in a subsample, we confirmed previous results but only for reasoning and attention and global cognition. Instead, PiL did not reveal clear associations with cognitive functioning.

Our findings regarding SoC add further new evidence to our previous study on the relationship between components of meaning in life and self-reported cognitive status, cognitive complaints, and classical proxies of CR (Bartrés-Faz et al., 2018).

In particular, they highlight the presence of an association between the psychological construct of SoC and cognitive functioning measured through formal neuropsychological assessments, as well as its mediator role on the relation between CR and cognition. As highlighted in the introduction, SoC is considered a psychological construct involved in resources control and the ability to manage these resources to better respond to environmental demands. Similarly, in its classical formulation, CR estimations were thought to reflect mechanisms that allow them to manage and optimally employ available resources to cope with brain changes and insults (Stern, 2009). Present results revealed that the association between these two constructs with cognitive functioning is not limited to some cognitive domains, but rather it seems to be spread across different cognitive functions. However, when we corrected for brain status, SoC was associated with global cognition and reasoning and attention, suggesting both general and specific effects on cognition of this construct. These findings parallel recent proposals considering that CR relates to better cognitive performance in multiple areas of cognition (Stern et al., 2018; van Loenhoud et al., 2020), and it is not specifically associated with executive functions, as initially proposed (Tucker and Stern, 2011; Roldán-Tapia et al., 2012).

Recently, Stern et al. (2018), using an iterative approach, identified a CR neural network that included brain regions forming parts of main large-scale networks, such as the default mode, the frontoparietal, and the salience networks (van Loenhoud et al., 2020), and was found to be involved in the execution of different cognitive tasks. Interestingly, its expression correlated with IQ, a proxy of CR, and crucially moderated the association between performance in some cognitive domains and other classical brain metrics, such as cortical thickness (Stern et al., 2018).

This evidence of a mediator role of CR on the relationship between brain measures and cognitive performance (see also Steffener et al., 2014) clearly suggested that CR not only acts as a mechanism that allows some individuals to better tolerate brain pathology (Stern, 2002) but also facilitates healthy individuals to perform better in cognitive tasks, possibly through promoting neural efficiency (Stern et al., 2018). To our knowledge, no studies have directly explored the neurobiological substrates of SoC at the level of brain network expressions; the cognitive findings may suggest that SoC may promote cognition through partial overlapping of neural underpins. In this regard, literature on neurobiology of stress suggests that prefrontal brain regions involved in emotional regulation, that, in part, overlap with those included in the salience network (Gupta et al., 2017), could be the neural substrate of SoC (Smith, 2002), in line with the hypothesis that these act on the brain and mental health *via* stress management and self-regulation mechanisms (Mc Gee et al., 2018). The only partial mediation effect of SoC on the relationship between CR and cognitive functioning, and the limited increase in the explained variance when it was included in the model as a mediator, suggested that the overlap between CR and SoC is restricted. In fact, when we adjusted analysis for a general neurodegeneration marker, we only see a mediator role of SoC for reasoning and attention (beyond global cognition), suggesting a specific effect only on some cognitive domains. Therefore, beyond the potential influence of SoC on classical proxies of CR (and vice versa) that could explain its mediation role for specific cognitive domains, its complexity as a psychological construct and its relationship with a broad variety of health-related outcomes suggest that it could act *via* independent protective mechanisms (e.g., stress reduction; Kimhi, 2015).

In contrast to SoC findings, PiL was not found to be associated with cognitive functioning in any of the domains considered. Initially, these results are contradictory to the previous investigations that looked at the relationship between PiL, cognition, and cognitive decline in aging. Results from Boyle et al. (2012, 2010) indicate that individuals with higher estimations of PiL are less prone to cognitive decline, MCI, and dementia, and they present better cognitive functioning in the presence of more brain pathology. In contrast to these previous investigations, including participants affected by MCI or in early or advanced stages of AD, we selected cognitive spared, middle-aged individuals and did not have follow-up data on cognitive changes. These methodological differences may account for the observed discrepancies in results. Hence, albeit speculative at this stage, this more future-oriented and motivational construct can exert a relevant role in promoting cognitive resilience in the presence of brain pathology and less impact, or no detectable relevance on cognitive outcomes, when considering normally performing individuals (however, see Merten et al., 2021, to explore the relationship between psychological wellbeing composite score, including PiL, and cognitive functioning and impairments).

Our present findings advocate for the inclusion of the construct of SoC as one of the factors potentially relevant for the study of CR and its relationship with cognitive functioning. This is in accordance with CR being a continuously evolving, dynamic concept, where the relevance of psychological and psycho-affective variables is accumulating (e.g., Marchant and Howard, 2015; Marchant et al., 2020). At a practical level, the incorporation of this kind of aspects in the study of the effect of CR on cognition may be highly relevant, considering that central concepts (such as the identification of intrinsic values that guide behavior, in the case of SoC) are usually amenable to psychological interventions (e.g., Hayes, 2016), therefore opening new avenues to promote reserve.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Fundació Unio Catalana Hospitals (code CEIC 18/07). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AP-L, DB-F, and JT participated in the initial conception of the design of the Barcelona Brain Health Initiative. GC and JS-S made substantial contributions to the actual design and implantation protocol. GC, JS-S, VA, and CP-G participated actively in the data collection and analysis. HZ supervised the blood biomarker measurements. KA-P, CP-O, SD-G, JT, DB-F, and AP-L contributed to the interpretation of the results. GC drafted the article. All authors made critical revisions, introducing important intellectual content, and final approval of the submitted version.

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The Assessment of Cognitive Reserve: A Systematic Review of the Most Used Quantitative Measurement Methods of Cognitive Reserve for Aging

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The cognitive reserve (CR) is widely accepted as the active ability to cope with brain damage, using preexisting cognitive and compensatory processes. The common CR proxies used are the number of formal years of education, intelligence quotient (IQ) or premorbid functioning, occupation attainment, and participation in leisure activities. More recently, it has employed the level of literacy and engagement in high-level cognitive demand of professional activities. This study aims to identify and summarize published methodologies to assess the CR quantitatively. We searched for published studies on PubMed, ScienceDirect, and Web of Science between September 2018 and September 2021. We only included those studies that characterized the CR assessment methodology. The search strategy identified 1,285 publications, of which 25 were included. Most of the instruments targeted proxies individually. The lack of a gold standard tool that incorporates all proxies and cognitive tests highlights the need to develop a more holistic battery for the quantitative assessment of CR. Further studies should focus on a quantitative methodology that includes all these proxies supported by normative data to improve the use of CR as a valid measure in clinical contexts.

Keywords: cognitive reserve, assessment, measurement methods, cognitive functioning, aging

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INTRODUCTION

The trajectories of typical aging are associated with a decline in several cognitive domains, whereas its expression is specific to each person. Some individuals undergo a precipitous deterioration, while others preserve their cognitive performance roughly intact, therefore presenting a successful aging (Stern et al., 2019). Besides, the heterogeneity of aging and its multiple forms of expression and

cases of recovery from brain injuries, as well as the delayed emergence of symptoms in the carriers of neurodegenerative diseases, raised the hypothesis of an underlying "reserve" that mitigates the expected cognitive impairment (Stern et al., 1992, 2019). This hypothesis quickly assumed primacy in the research field, evolving for the discussion of constructs such as compensation, brain maintenance, brain reserve (BR), cognitive reserve (CR) and resulting in new approaches, methods of assessment, theoretical definitions, and exploration of their impact in human cognition (Stern et al., 1992, 2019).

From all explanatory models, BR and CR offer greater consensus. The BR refers to a passive model that states that normal cognitive functioning is sustained by neuronal subtracts that, when depleted to a critical threshold, become insufficient to maintain it (Stern, 2009, 2012; Cashman, 2011). At the same time, CR is widely accepted as the active ability to cope with brain damage, using preexisting cognitive and compensatory processes (Stern, 2009; Larson et al., 2013). During the past 3 years, there was a joint effort to develop a consensual definition, as well as research guidelines for CR, achieved through focus workgroups, consultation from expert investigators, workshops, and research studies. This framework helps design and implementation of studies in the field of CR, brain maintenance, and BR (Collaboratory on Research Definitions for Cognitive Reserve and Resilience, 2018). In the words of the NIH-collaboratory workgroup, the CR "is a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease"[1]. The flexibility and plasticity of cognitive networks, as well as the molecular and cellular mechanisms, help the brain to actively cope with age-related changes and diseases (e.g., neurodegenerative diseases; Stern, 2002; Stern et al., 2019; see Text Footnote 1). In other words, alternative networks are used to successfully complete a task or maintain normal daily performance. This is a compensatory process that reflects personal CR (Stern, 2006), and is also investigated by previous brain-imaging findings that support the cognitive performance in older adults (Davis et al., 2008). Being an active model, it is assumed that CR is influenced by various factors (e.g., life experiences, participation in stimulating environments, and education) that increase brain plasticity and resistance to cellular death (Stern, 2009; Kivimäki et al., 2015) and other age-related phenomena (e.g., synaptic and white matter changes, pathological modifications, etc.; Taylor et al., 2007; Kim et al., 2019). In fact, several studies report lower rates of cognitive decline and reduced risk of developing dementia among individuals with higher premorbid IQ, higher educational level, that engaged in leisure activities and enrolled in more cognitively demanding professional activities (Stern et al., 1994; Deary et al., 2004; Zahodne et al., 2015). CR minimizes the early expression of clinical cognitive symptomatology in brain pathology where a greater pathological load is necessary to observe the same degree of dementia symptoms in those with higher CR (Stern, 2006; Solé-Padullés et al., 2009; Mondini et al., 2016; Osone et al., 2016). Therefore, a faster decline is expected when the CR overload has been reached, with the emergence of behavioral symptoms even before a search for a possible positive biomarker's result (Alves et al., 2012; Steffener and Stern, 2012; Jansen et al., 2015; Kivimäki et al., 2015; Mondini et al., 2016; Groot et al., 2018). In summary, the individual level of CR has been strongly associated with the maintenance of cognitive health and an active lifestyle during aging, impacting the mitigation of Alzheimer's disease symptomatology (Clare et al., 2017; Persson et al., 2017). In cases where a better cognitive performance was observed, it is important to ensure that those differences come from longitudinal measurement results (see Text Footnote 1).

Despite its greater involvement in cognitive functioning, the objective measurement of CR remains one of the biggest challenges in the field. This is mainly due to the complexity of the CR construct that makes it difficult to operationalize. Again, on the framework of the NIH-collaboratory workgroup, we found general considerations and guidelines to deal with the CR assessment. Ideally, the CR measure should include a variable that represents the moderation of the relationship between the life course-related brain changes and the changes in cognition. The accuracy of CR measurement will be higher whenever other measures are included: (i) measures of anatomic changes (e.g., brain-imaging analysis), (ii) measures of cognition (e.g., cognitive performance and daily functioning), and (iii) CR proxy, referred to the variable that influence the relationship between (i) and (ii). This last hypothesized mechanism (CR proxy) is commonly addressed by several sociobehavioral proxies, namely the number of formal years of education, intelligence quotient (IQ), occupation attainment, and participation in leisure activities (see Text Footnote 1). Recently, it has also included the level of literacy and the engagement in high-level cognitive activities (Stern, 2009, 2012; Schoenberg et al., 2011; Larson et al., 2013; Malek-Ahmadi et al., 2018). These two last variables actively contribute to the CR, since they remain dynamic throughout life, including after the completion of formal education (Malek-Ahmadi et al., 2018; Thow et al., 2018).

Considering the difficulty in achieving adequate methods for assessing CR, some authors utilized functional imaging to analyze networks and processes likely to be involved in CR (van Loenhoud et al., 2018; Stern et al., 2018, 2019). This approach provided a better understanding of the neural mechanisms of CR, allowing the identification of relevant proxies to include in scales and questionnaires, as surrogates of the underlying brain mechanisms of CR, therefore constituting an indirect measure of this construct.

Measures of the CR vary from instruments that use one single proxy, often education (Chapko et al., 2018), to tools that include several proxies either converted into a total score or developing latent variable models (generally by principal component analysis or structural equation modeling; Conroy et al., 2010; Giogkaraki et al., 2013). The approach of using one single proxy is likely to disregard important components of a complex construct as the CR. Therefore, questionnaires that comprise multiple components seem to be the way of standardizing the CR assessment.

According to our knowledge, there is only one recent systematic review looking for properties of CR questionnaires,

[1]https://reserveandresilience.com/framework/

conducted by Kartschmit et al. (2019). They concluded about the lack of measurement quality, considering the content and structural validities, as well as responsiveness (Kartschmit et al., 2019). Similarly, Landenberger et al. (2019) also concluded about the lack of validity and the need for cross-cultural adaptation of the scales and questionnaire used to measure CR. This study aims to summarize the most used quantitative measurement methods of CR for aging, considering the post-search period of Kartschmit et al. (2019) study.

METHODOLOGY

Literature Search

We conducted searches for studies published between September 2018 and September 2021, considering the last systematic review by Kartschmit et al. (2019). The search terms used were "reserve" or "reserves," "cognition," or "brain," "questionnaire" or "instrument" or "tool," "cognitive reserve," or "neuropsychological assessment." Searches were limited to peer-reviewed publications and conducted in the following databases: Web of Science (Web of Science Core Collection, Current Content Connect MEDLINE, and SciELO), ScienceDirect, and PubMed.

Eligibility Criteria

We only included human studies that reported at least one quantitative measure (e.g., questionnaire or tool) of CR, regardless of the presentation of its psychometric properties. We did not impose restrictions regarding the study populations and diseases, once describing the presence of ways to assess the CR. We also included any settings, i.e., clinical or research contexts. No language restrictions were made.

We excluded studies that only used sociodemographic variables to address the CR (e.g., age and educational level). Systematic reviews, meta-analyses, conferences, and workshops were also excluded, as well as articles that discuss the impact of their main goal in the CR, without describing the ways to assess it. Finally, we excluded studies related to children and adolescents (age < 18 years), but no other age restrictions were applied.

Study Selection

Two authors (JN and BG) screened the papers and assessed them, considering the eligibility criteria. Both researchers worked independently in the abstract inspection. The discrepancies were discussed and solved by consensus. The selection process is presented in **Figure 1**, according to the PRISMA guidelines (Page et al., 2021).

RESULTS

Notably, 25 out of 579 studies screened for analysis met the inclusion criteria and were included in this study. Considering these 25 studies, the following questionnaires were the most frequently used: the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012), the Cognitive Reserve Questionnaire (CRQ; Rami et al., 2011), the Lifetime of Experiences Questionnaire (LEQ; Valenzuela and Sachdev, 2007), the modified version of Cognitive Reserve Scale [CRS (Leon et al., 2011), mCRS (Relander et al., 2021)], and the Cognitive Reserve Assessment Scale in Health (CRASH; Amoretti et al., 2019). Besides, four articles also included cognitive scales to assess premorbid functions.

Next, we describe the quality criteria for each way of the CR measurement: questionnaires and cognitive scales.

Measurement Through Cognitive Reserve Questionnaires

Only 21 articles from 25 studies used questionnaires to address the CR. The major part of the questionnaires combined several sociodemographic characteristics (e.g., age and educational level) with daily living and intellectual and professional activities (refer to **Supplementary Table 1**).

Different instruments were used to assess CR in both healthy and clinical populations, sorted from most to least used: of 25 studies, 12 used the CRIq, 2 studies used the CRQ, 2 studies used the LEQ, 1 study used the CRASH, and 1 study used the mCRS (refer to **Supplementary Table 1**).

The CRIq is widely used in the field of CR assessment, with 14 cultural validation[2] (the Turkish version presented in **Supplementary Table 1**) and two computations (in English and Italian versions). In this study, the CRIq was the most used questionnaire that considers validation studies and experimental approaches. Its worldwide use is an asset, since there are several validations that allow for the comparison between studies. The CRIq was composed of 20 items, which were divided into three sections, namely, CRI-education, CRI-working, and CRI-leisure time. The CRI-education was assessed based on the years of schooling. The CRI-working activity section categorizes the professional activities into five levels, i.e., from unskilled labor to management positions. If the person changes professional activity, it should be classified into a 5-year period according to the new level of employment. For the CRI-leisure times, the activities were grouped based on the frequency as follows: weekly (e.g., reading newspapers), monthly (e.g., cinema or theater), and annual frequency (e.g., exhibitions, concerts, and conferences). The CRI-leisure times also includes activities performed at a fixed frequency, such as caring for pets. Finally, the CRIq does not assess different stages of life separately.

The LEQ was the second most used questionnaire. This questionnaire is usually used in the field of aging, since it was specifically developed for participants aged $\geq$ 65 years. The LEQ is composed of 42 questions and includes measurements of educational, occupational, and cognitive lifestyle activities at different stages of life. Compared with CRIq, the LEQ has two main disadvantages: (1) the time of administration (approximately 30 min, whereas the CRIq takes 10–15 min) and (2) the exclusion of other age groups. However, since it was specifically developed for aging, the LEQ appears to have an advantage, which is the characterization of the previous states of functioning.

[2]https://www.cognitivereserveindex.org/

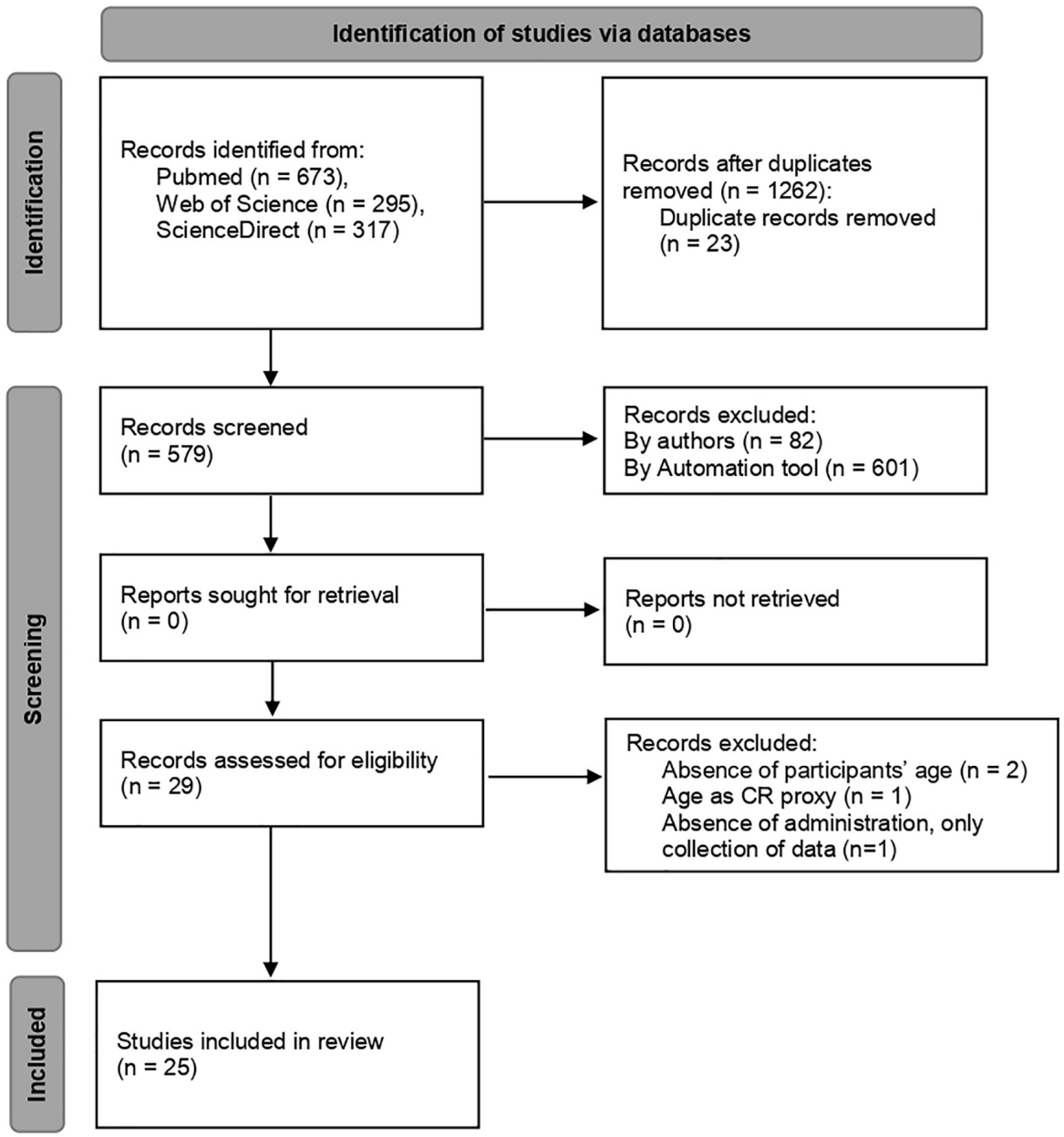

FIGURE 1 | Flowchart of literature review.

The CRQ was the third most used questionnaire in the selected studies. This questionnaire is widely used in the clinical field, especially in dementia, since it takes a few minutes to complete (Amoretti et al., 2019). It is composed of eight items that address personal schooling, training courses, parents' schooling, professional occupation, music training, and languages proficiency. Despite its advantage of the short time of application and the scoring system based on a simple summing, the CRQ has several limitations concerning the assessment of CR, for example, the questionnaire neither evaluates different stages of life or includes a variety of leisure activities nor counts the type of courses taken or previous states of functioning.

The mCRS is a modified version of the CRS that composed of 24 items from the original version, including 20 questions about schooling and information seeking, hobbies, and social relationships. This modified version was proposed by Relander et al. (2021), who excluded the items of activities of daily living and modified some others to capture activities such as spectating sports or nature hobbies. It also includes an assessment of the frequency of those activities in different life stages. As a result, although the mCRS has the advantage of gathering information

throughout life, it also has some limitations that it does not consider educational and professional attainment. The CRASH was developed specifically for severe mental illnesses, which is the major advantage of this scale for those willing to address the CR in this population. It only takes 10 min to complete the application. This scale includes the assessment of education, occupation, and intellectual and leisure activities. All domains have the same weighting in the final score, which is achieved by a formula.

Besides these questionnaires, there are four articles that used other measures (**Supplementary Table 1**). Dekhtyar et al. (2019) were interested in the assessment of the complexity of professional occupations, the satisfaction of social connection, and the mental, social and physical activities, besides the level of education. For this purpose, they used their own indexes, considering several stages of life span. Belleville et al. (2019) combined an adapted version of the CRQ for French with the educational level. The authors used a cognitive training program that include videogames, and so they also assessed music and game experience, multilingualism, and computer proficiency. In fact, this complimentary assessment also translates to some part of CR, since it corresponds to extra activities in addition to educational level. Darwish et al. (2018) were specifically interested in the impact of education and occupational attainment, two accepted CR factors, in the development of dementia. For this purpose, they used the International Standard Classification of Education (ISCED-11; UNESCO, 2012) and the International Standard Classification of Occupations (ISCO-08; ILO, 2012). The remaining proxies of CR were addressed using a sociodemographic questionnaire of the Dementia Research Group (DRG; Darwish et al., 2018). Finally, Szepietowska (2019) investigated the relationships between CR, the severity of depression, and cognitive functioning. Due to the lack of Polish methods to assess CR, the CRIq was used. This questionnaire contemplates a subjective assessment of life activities, formal educational level, and the nature of the occupational activity (Szepietowska, 2019).

Measurement Through Cognitive Scales

Only four articles from 25 studies used cognitive scales to address this topic, revealing premorbid functioning as an important factor for CR. Three studies used the National Adult Reading Test (NART, Grober et al., 1991; and French adaptation of National Adult Reading Test (fNART), Mackinnon et al., 1999), and one study used the Multiple Choice Word test (MWT-B, Lehrl et al., 1995). Besides premorbid functioning, Pettigrew et al. (2019) also assessed crystallized domains, using the vocabulary scores of Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981).

Pettigrew et al. (2019) used premorbid functioning (through NART), crystallized domains (through vocabulary, WAIS-R), and educational level to address the CR. These 3 measures were combined into a final score using *z*-scores and its average (Pettigrew et al., 2019). van Loenhoud et al. (2018) also used a reading test to address the CR, but they did not report others CR proxies. The MWT-B was used by Gajewski et al. (2020), which is a word meaning test that addresses crystallized intelligence. The IQ is addressed by the number of correct identification of meaningful words (Gajewski et al., 2020). They also used the years of education to complete the assessment of CR, similar to the study by Pettigrew et al. (2019).

Cognitive Reserve Assessment Settings and Study Population

As stated earlier, our search for CR assessments comprised both clinical and research contexts. In general, the healthy population included in the selected research studies ranged between middle and old healthy aging, with an exception of van Loenhoud et al. (2020) who assessed participants aged 20–80 years. Regarding the cognitive assessments, most of the studies considered reading and vocabulary tests (i.e., NART, fNART, and vocabulary) administered to middle-aged participants. The MWT-B was applied from middle-aged to older healthy participants (Gajewski et al., 2020). Finally, the NART was also used in younger participants looking for contents that contribute to CR, considering this wide range of ages (van Loenhoud et al., 2020).

For clinical sample studies, different CR questionnaires were chosen, considering several pathologies. The CRIq was used in outpatient cohorts of multiple sclerosis (Ifantopoulou et al., 2019; Artemiadis et al., 2020), severe acquired brain injury (sABI; Bertoni et al., 2020), dementia due to Alzheimer's disease (Montemurro et al., 2018), and substance use (Toledo-Fernández et al., 2020). The LEQ was administered to patients with the behavioral variant of frontotemporal degeneration (bvFTD; Kinney et al., 2021) and dementia (Paplikar et al., 2020). The CRQ was used in specific autoimmune encephalitis (Sola-Valls et al., 2020), and severe mental illness, as well as the CRASH, specifically developed for these cases (Amoretti et al., 2019).

DISCUSSION

The most accepted concept of CR is based on the theory developed by Stern (2009), but the consensus about a universal definition and the factors that should be considered for its measurement is still in discussion. However, revealing the complexity of the construct, it is assumed that the assessment should include at least one factor besides the educational level, given that schooling is an idiosyncratic feature that does not remain dynamic throughout life. For this purpose, we excluded all the papers that addressed the CR by a single proxy (e.g., educational level; Alattar et al., 2020), despite the fact that it is the easiest way to assess it in clinical populations (e.g., Alzheimer's disease; Kwak et al., 2020).

In this study, we included studies that used quantitative measures of CR, which means questionnaires, scales, and/or cognitive tests that result in a total score that hypothetically corresponds to an individual level of CR. In contrast, we did not analyze the development of those tools or the measurement properties of the questionnaires or scales, since it was already analyzed by Kartschmit et al. (2019). We intend to summarize the quantitative methodologies used to assess the CR during the past years, discussing its instructions, scoring systems, target populations, advantages, and limitations.

We divided the articles based on those that used questionnaires and those that used cognitive scales. Regarding the measurement by questionnaires, the articles were included whenever the authors described what type of questionnaire or, preferably, the specific one that they used. We also included studies that described other quantitative ways to assess the CR, even without the use of a specific questionnaire. In those cases, the authors reported indexes or several questions as potential indicators of a personal level of CR, for example, the proficiency in languages (Narbutas et al., 2019) or social network (Dekhtyar et al., 2019). Except for the questionnaires that were specifically developed for a target population or clinical condition (e.g., CRASH for severe mental illness; Amoretti et al., 2019), most of them were used in more than one study. This means that the CR already has assessment methods that have been disseminated and validated in the scientific community for different countries. In this review, CRIq was the most used questionnaire among the reviewed articles. Considering its unrestricted life span, this questionnaire was unable to assess the specific period of time when the activities have been performed by the participants, which means it may not be answered considering the more active and functioning stage. Since the CR is intended to be a construct that is partially stable throughout life, it is important to consider the best personal time of functioning to achieve the most consistent individual level of CR. As a result, if the instructions were not provided to ensure a response related to the best functioning or more active stage of life, probably the personal level achieved does not correspond to the better persons' level, especially in populations with memory impairment. In that case, the LEQ has the ability to specifically address earlier stages of life, since it is divided into three stages (between 13 and 30 years, from 30 to 65 years, and from 65 years). However, due to its time of administration, the LEQ is difficult to implement in clinical practice. This disadvantage of unrestricted life span is also presented in the CRQ, with the limitation of its short composition addressing a general content of a personal CR level. However, the CRQ has a 6-point Likert-type scale instead of dichotomous answers used in CRIq, which allows the measurement in terms of frequency or proficiency considering the question at hand. The same response option is used in LEQ as well as open questions. The major advantage of the CRQ in comparison with both LEQ and CRIq is the short application time for the clinical population, since it has just 8 questions and takes only 3 min (Rami et al., 2011; Sobral et al., 2014, 2015; Harris et al., 2015).

The CRIq was used in more than one disease, ranging from neurodegenerative conditions (e.g., dementia due to Alzheimer's disease; Montemurro et al., 2018) to substance use (Toledo-Fernández et al., 2020). Recently, Stern et al. (2019) endorsed the term "cognitive resilience" as a combination of BR, CR, compensating, and brain maintenance. In clinical cases, this cognitive resilience helps to deal with aging and mitigates the impact of symptoms due to neurodegeneration (Stern et al., 2019). As a part of cognitive resilience, the use of CR assessment on clinical population is crucial to detect both people with low CR, and, consequently, with less neural resources to deal with the disease as well as those with higher levels of CR, who benefit from the mitigating effect on behavioral symptomatology. To optimize this assessment, mostly in clinical populations, it is important to obtain information about previous cognitive status, which is often not accessible. Frequently, premorbid intelligence is the indirect means to address it and plays an important role in the diagnosis of cognitive decline. Furthermore, it is also considered as a proxy of CR (Lezak et al., 2012). Therefore, several authors include neuropsychological tests to assess both premorbid and general cognitive functioning, when addressing the personal level of CR (Thow et al., 2018; Zijlmans et al., 2021). More specifically, Zijlmans et al. (2021) investigated the CR by creating a latent variable that captures variance across five cognitive tests and an MRI-inferred analysis.

However, it is important to point out the exclusive use of cognitive tests as a limitation, since it excludes the assessment of lifestyle activities that are actively involved in the CR and are usually assessed by dedicated questionnaires. Considering the complexity of the CR construct, a perfect model of assessment should include cognitive scales to address premorbid functioning and/or crystallized domains (reading and vocabulary tests, respectively), and questionnaires focusing on education, professional activities, leisure time, and social life. The approach of Thow et al. (2018) incorporating the LEQ for the assessment of life experience information and the estimated full-scale IQ (through WTAR; Thow et al., 2018) is a paradigmatic example. Likewise, the battery proposed by our group and developed specifically for the assessment of CR (Battery for the Assessment of Cognitive Reserve, BARC) has the rational of combining several questionnaires and cognitive scales computed into a single score (Nogueira et al., 2020). Ideally, the most complete paradigm of CR should include life experience information, cognitive tests, and MRI analysis. With this review, we want to emphasize that most of the instruments evaluated targeted proxies individually and between those (i) the LEQ represents a promising questionnaire to assess CR due to its extensive structure, which contains many different CR proxies, with the limitation of not addressing cognitive domains; (ii) the CRIq was the most translated CR questionnaire, which favors a further comparison between studies; (iii) the CRQ was limited in its structure but is quite simple to use in large samples or epidemiologic studies; and (iv) the two main cognitive domains considered crucial for CR assessment were the crystallized domains and premorbid functioning.

As a final statement and future perspectives concerning CR assessment, the lack of a gold standard tool, incorporating all proxies and cognitive tests, emphasizes the need to develop a more holistic battery for the quantitative assessment of CR. Further studies should focus on a quantitative methodology that includes all of these proxies and is supported by normative data to improve the use of CR as a valid measure in clinical contexts.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/ **Supplementary Material**,

further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JN and SF contributed to the conception and design of the study. JN and BG organized the database and performed the selection and screening analysis of the articles. JN wrote the manuscript. MS, IS, and SF reviewed the methodology implemented and the results. All authors contributed to manuscript revision, read it, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.847186/full#supplementary-material

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M/EEG Dynamics Underlying Reserve, Resilience, and Maintenance in Aging: A Review

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Cognitive reserve and resilience refer to the set of processes allowing the preservation of cognitive performance in the presence of structural and functional brain changes. Investigations of these concepts have provided unique insights into the heterogeneity of cognitive and brain changes associated with aging. Previous work mainly relied on methods benefiting from a high spatial precision but a low temporal resolution, and thus the temporal brain dynamics underlying these concepts remains poorly known. Moreover, while spontaneous fluctuations of neural activity have long been considered as noise, recent work highlights its critical contribution to brain functions. In this study, we synthesized the current state of knowledge from magnetoencephalography (MEG) and electroencephalography (EEG) studies that investigated the contribution of maintenance of neural synchrony, and variability of brain dynamics, to cognitive changes associated with healthy aging and the progression of neurodegenerative disease (such as Alzheimer's disease). The reviewed findings highlight that compensations could be associated with increased synchrony of higher (>10 Hz) frequency bands. Maintenance of young-like synchrony patterns was also observed in healthy older individuals. Both maintenance and compensation appear to be highly related to preserved structural integrity (brain reserve). However, increased synchrony was also found to be deleterious in some cases and reflects neurodegenerative processes. These results provide major elements on the stability or variability of functional networks as well as maintenance of neural synchrony over time, and their association with individual cognitive changes with aging. These findings could provide new and interesting considerations about cognitive reserve, maintenance, and resilience of brain functions and cognition.

Keywords: aging, cognition, M/EEG, dementia, connectivity

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INTRODUCTION

Understanding the evolution of cognition as we age is crucial not only because it is intimately related to everyone's subjective experience, but to help describe and better understand cognition itself. Cognitive aging is a highly variable phenomenon, characterized by a decline in cognitive abilities that might lead to higher risk of pathological aging in some individuals, whereas others are able to remain efficient in most everyday tasks until an advanced age (Reuter-Lorenz and Park, 2014). Research on the variability of age-related changes across individuals aims at answering several questions, such as the factors associated with preserved cognitive functioning with age (the "*why*" question), or what differs between individuals with preserved vs. declined cognitive

performance (the "*how*" question). While lifestyle activities associated with reduced risk of cognitive decline and pathological aging have been extensively investigated and specified (see Livingston et al., 2020, for a recent review), a mechanistic understanding of the neural bases underlying individual differences with advancing age remains to be further developed. Achieving this goal requires the use of highly sensitive methods, and the investigation on brain activity with high spatial and temporal resolutions.

The concept of cognitive reserve has originally been proposed to improve our understanding of mechanisms underlying sustained cognitive performance in spite of age-related and pathology-related brain changes (Stern, 2002). Over the last two decades, this concept has undergone several changes and developments (see Cabeza et al., 2018; Stern et al., 2020; Pascual-Leone and Bartres-Faz, 2021). The current concepts of maintenance, resistance, and resilience have been proposed to specify the heterogeneity brain and cognitive changes in face of aging and neurodegenerative disease. During healthy aging, *maintenance* (Nyberg et al., 2012) refers to the relative absence of brain changes with advancing age, whereas *reserve* (Stern, 2002) encompasses the compensatory processes allowing the preservation of cognitive performance in the presence of structural and functional brain changes. The concept of reserve involves two complementary aspects, namely, brain reserve (i.e., individual differences in brain size, number of synapses, etc.) and cognitive reserve (i.e., individual differences in the cognitive processes and brain networks recruited to perform a given task). With the progression of neurodegenerative disorders, *resistance* (Arenaza-Urquijo and Vemuri, 2018) defines the protection of brain reserve against alterations and the prevention of brain lesions and damages before their occurrence. Finally, *resilience* (Pascual-Leone and Bartres-Faz, 2021) concerns the processes involved in the compensation of changes occurring with the development of neurodegenerative disorders, explaining various degrees of symptomatology in the face of an equal pathological load. Some degree of overlap may exist between these concepts. As an example, compensatory adjustments (e.g., increased frontal recruitment) might be implemented in the presence of both age- and pathology-related changes, yet qualitative differences may also be observed between the adjustments implemented in response to healthy aging and pathology. A recent review of Pascual-Leone and Bartres-Faz (2021) specified these concepts and emphasized the need for individually based markers that could predict an individual's risk for disability and cognitive decline.

Neuroimaging studies have been central in the emergence and evolution of the concepts of reserve, maintenance, and resilience. Several decades of work aimed at investigating structural (i.e., gray matter, white matter) and functional (i.e., local activity, association between the activities of distinct brain regions) changes with age and pathology (e.g., Damoiseaux, 2017; Spreng and Turner, 2019). Recent work revealed that these dimensions are closely related, with large-scale brain functional network relying on a structural architecture of white matter fibers (e.g., Hinault et al., 2019; Suárez et al., 2020). Indeed, preserved brain integrity has been associated with preserved cognitive functioning. This work also identified compensatory adjustments in older adults (i.e., larger activations, bilateral recruitment) associated with similar cognitive performance to that of younger individuals (e.g., Cabeza et al., 2018). These studies mainly relied on high spatial resolution methods such as functional magnetic resonance imaging (fMRI), characterized by excellent spatial accuracy but low temporal resolution (in the order of seconds). Therefore, the temporal dynamics of brain networks and the influence of age and pathology on these dynamics remain poorly known. Investigating these dynamics with high temporal resolution methods (in the order of milliseconds) such as magnetoencephalography (MEG) or electroencephalography (EEG) is important because higher cognitive functions such as memory and cognitive control that are most affected by age and pathology involve multiple cognitive processes in rapid successions and short durations (e.g., Courtney and Hinault, 2021). Even when compensation may mask these changes in clinical or neuropsychological assessment, specifying dynamic network connectivity may reveal alterations in the stability of communications between brain regions or delays in the fast succession of connectivity patterns, providing a better understanding of the concepts of reserve, maintenance, resilience, and resistance.

The brain generates its own temporal structure, which is critical to the ways in which signals are routed, combined, and coordinated (e.g., Bao et al., 2015; Voytek and Knight, 2015). Brain rhythms present the particularity of being observed across species (e.g., Buzsáki, 2019), which suggest a major evolutionary advantage of rhythmic communications (e.g., Miller et al., 2018). Brain rhythms are distinguished in different frequency bands [delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), gamma (30–45 Hz)]. MEG and EEG methods enable the investigation of these rhythms and dynamic connectivity patterns in humans (e.g., Baillet, 2017). Given the critical involvement of coordinated brain rhythms in higher-order cognitive processing, age-related changes in the dynamic of brain communications may act as a marker for cognitive decline in older adults. Such complex interplay across rhythms is highly sensitive to structural changes and the progression of neurodegenerative disorders (e.g., Gaubert et al., 2019; Courtney and Hinault, 2021) as even small changes of dynamic synchrony can lead to cognitive decline with aging (e.g., Hinault et al., 2020, 2021; Kumral et al., 2020).

In this study, we reviewed EEG and MEG studies in healthy older individuals and in patients to identify elements that shed new light on cognitive aging and pathology effects. We focused on three main patterns, namely, (1) compensatory or resilience adjustments when brain dynamics are altered, (2) maintenance of these dynamics in the face of aging or pathology, and (3) non-effective or maladaptive changes related to normal aging or pathology. These concepts have been extensively investigated with fMRI; we thus aimed at highlighting the complementary contribution of M/EEG findings. M/EEG can indeed detect between-group differences in the initiation, maintenance, or interruption of brain communication at the sub-second level, which is therefore highly sensitive to early disruptions associated with age and pathology. In this review, we first presented studies contributing to these concepts in healthy aging before presenting

work on pathological aging. Given the work conducted in pathological aging, we focused on Alzheimer's disease (AD) and its preclinical stage the mild cognitive impairment (MCI). We concluded with recommendations and future directions that could guide and stimulate future studies. Such endeavor could lead to new cognitive stimulations strategies targeting brain rhythms and reduce the cognitive decline commonly associated with age.

NORMAL AGING

Nineteen M/EEG studies, including younger (20–30 years) and older (60–85 years) healthy participants, have been selected, investigating cognitive performance and neural synchrony data (see **Table 1**). In this study, we described three of the most commonly used techniques. First, the phase-locking value (PLV; Lachaux et al., 1999) measures whether the oscillatory phase of the activity of a group of neurons, in a certain frequency band, can transiently synchronize with those of another group of neurons. This transient phase locking has been associated with communications between neural groups (Fries, 2015). A second technique similar to this is the phase lag index (PLI; Stam et al., 2007), which measures the asymmetry of the distribution of phase differences between two signals. Finally, coherence (Nunez et al., 1997) measures the association of signals' amplitudes across brain regions. These measures and provides information about neural synchrony and the presence of functional connectivity between brain regions. The main results studied in this section are illustrated in **Figure 1A**.

Compensation

In older individuals with similar levels of cognitive performance as younger individuals, previous MRI studies have shown that older individuals frequently engage additional brain regions, as described in the Compensation Related Utilization of Neural Circuit Hypothesis (Reuter-Lorenz and Cappell, 2008) model. This increased recruitment of brain regions has been associated with cognitive performance and is referred to as compensation (Cabeza et al., 2018). Angel et al. (2010, 2011) investigated this phenomenon in EEG using event-related potential (ERP). They revealed larger bilateral activity in older individuals with higher cognitive performance. M/EEG studies critically identified that an increased synchronization of frontoparietal regions has been observed in older individuals showing preservation of cognitive functioning. Ariza et al. (2015) asked healthy young and elderly participants to perform an interference-based working memory task in which participants were asked to memorize a face/sound pair (a face was displayed and associated with a semantic attribute). The pair was followed by an interference phase during which a known face with a question about that person was presented to them. Finally, a recognition phase in which participants were asked to tell whether the presented pairs were the same as those presented in the encoding phase. This study reported a global increase in alpha synchrony (measured by PLV) in older individuals compared to younger individuals, whereas both groups showed similar cognitive performance. This increased alpha synchrony has only been observed during the interference period and has been interpreted as a compensatory mechanism in older individuals.

Using an inhibitory task, Hong et al. (2016) showed that an increase in phase synchrony of the delta and theta frequency bands localized at the frontocentral and parietocentral areas reflected a compensatory phenomenon in healthy older individuals (see also Phillips and Takeda, 2010, for similar findings in the gamma frequency band). Also, a posterior-anterior synchrony switch (increase in delta synchrony in anterior vs. posterior position) was also found to be compensatory for a facial emotion recognition task (Aktürk et al., 2020). These compensatory phenomena are found not only in cognitive tasks but also in motor tasks. For example, Rosjat et al. (2021) showed increases in delta and theta synchrony (measured by PLV) in healthy elderly in association with sustained motor performance at the same level as in young people (see also Rosjat et al., 2018).

Maintenance

Increased brain activity is not systematic, and it is important to note that some individuals do not need to implement these compensations, possibly because of higher cognitive reserve levels (Stern, 2009). López et al. (2014b), in a study comparing the global connectivity (with PLV and PLI) of older participants with higher or lower cognitive reserve, showed compensatory phenomena from the latter group only. Indeed, while cognitive performance was similar between low and high reserve participants, individuals with lower reserve showed an increase in theta, alpha, and beta synchrony in frontal, temporal, and occipital regions. This suggests that some individuals show a more efficient network functioning and therefore do not need to engage a more extended brain network. Relatedly, Ho et al. (2012) showed that lower theta and alpha synchrony levels (measured with coherence and phase-locking measures) in the parietal region were associated with similar performance than younger individuals.

Maintenance thus refers to the preservation of similar brain activity levels than younger individuals, allowing cognitive abilities to be relatively preserved with advancing age (Nyberg et al., 2012). MRI work showed, for example, that older individuals with little changes in functional activity during encoding, relative to younger adults, can sometimes perform better than older individuals with larger activation changes (Düzel et al., 2011). Studies on this phenomenon are, to our knowledge, rare. Rondina et al. (2019) investigated the preservation of brain dynamics with aging, using a spatial memory task where participants were asked to remember the spatial location of three objects seen separately. In the test phase, participants were then asked to determine whether the location of the objects was the same or different than in the memory phase. They revealed that older individuals showed a similar pattern of brain activations than young participants, with an increase in theta band oscillatory activity in occipital regions and a decrease in frontotemporal regions. The maintenance of this brain activity pattern was associated with similar cognitive performance between age groups. Also, in a visual attention task, young and older individuals

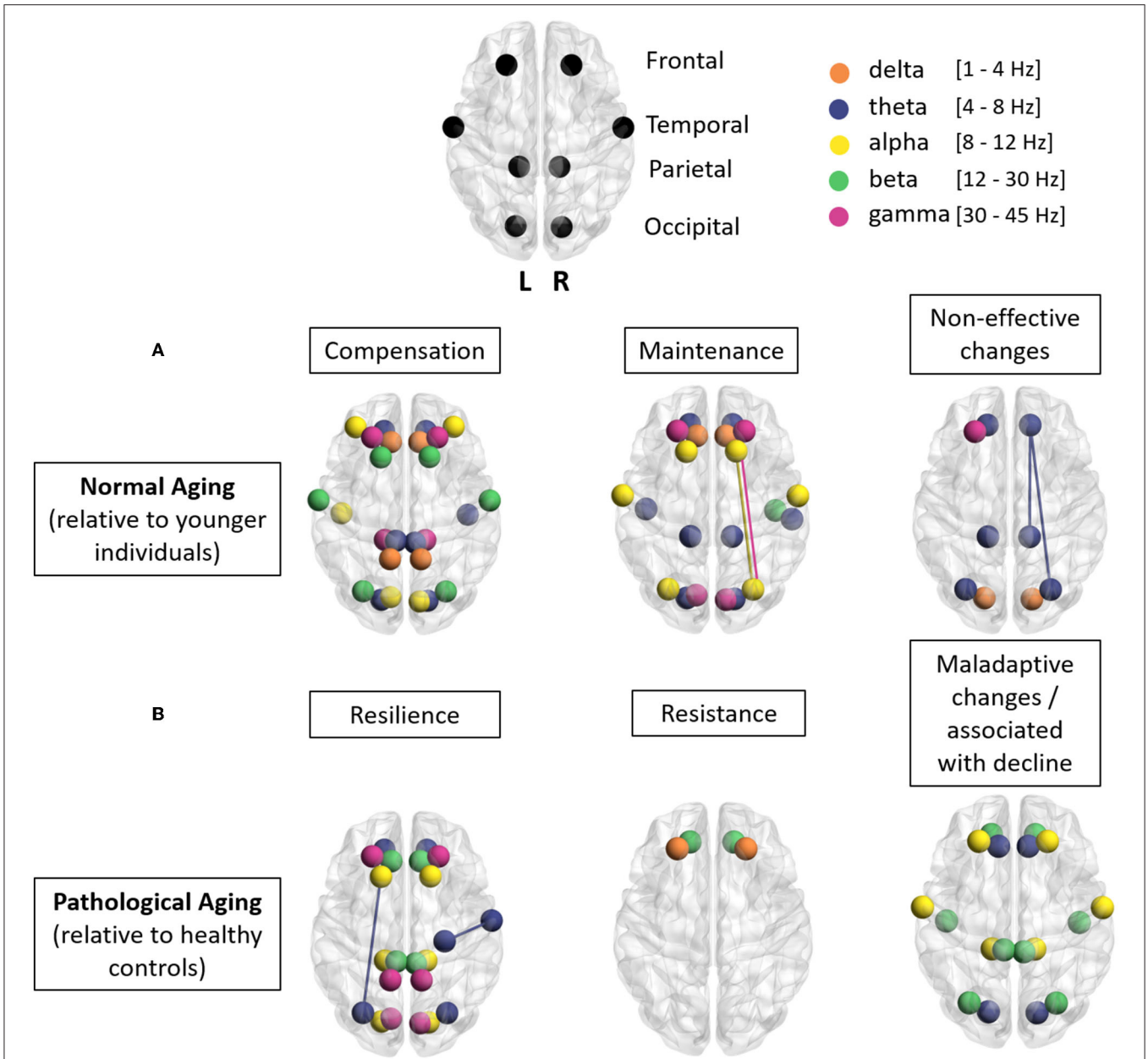

FIGURE 1 | Illustration of the main results of this study: each point represents a brain region and each color a frequency band (orange, delta; blue, theta; yellow, alpha; green, beta; pink, gamma). **(A)** Normal aging. This row of three brains summarizes the main results found in this review (change in synchrony in different regions for different frequency bands relative to younger individuals) for the notions of compensation, maintenance, and non-effective changes in normal aging. **(B)** Pathological aging. This row of three brains summarizes the main results found in this review (change in synchrony in different regions for different frequency bands, relative to healthy controls) for the notions of resilience, resistance, and maladaptive changes in pathological aging. Using BrainNet-viewer tool (Xia et al., 2013).

showed a similar pattern of increased lower gamma frequency activity in the frontal region with increasing task difficulty (Phillips and Takeda, 2010). Moreover, Coquelet et al. (2017) investigated MEG phase synchrony at rest and reported maintenance of the electrophysiological connectome with age. Coquelet and colleagues observed similar patterns between age groups in the alpha and beta frequency bands. The maintenance of synchrony in the beta band was positively correlated with the maintenance of cognitive performance in older individuals.

This functional maintenance seems to critically depend on the maintenance of the underlying structures of the brain networks. Hinault et al. (2020) investigated the structure-function relationship between diffusion tensor imaging (DTI) and EEG data of neuronal synchrony (PLV) of young and old healthy participants. The authors used an arithmetic task,

in which participants had to maintain, or update, arithmetic operations (addition, multiplication) in working memory to determine whether the proposed equation results (e.g., $8 \times 4 = 36$) were correct or incorrect. Preserved integrity of white matter fibers at a similar level to younger participants, in some older individuals, was associated with preserved functional synchrony in the alpha and gamma frequency bands, and similar cognitive performances between age groups. In particular, the inferior fronto-occipital tract was associated to functional coupling between the inferior frontal gyrus and the occipital lobe. These results also illustrate the strong association with the preservation of brain reserve, which would enable such maintenance (Stern, 2009).

Thus, the maintenance of functional synchrony with age (at rest and during task completion) is associated with the preservation of cognitive functions in healthy elderly individuals. This maintenance has mainly been observed between frontal and parietal regions. However, the preservation of this functional synchrony at a similar level to younger individuals is frequently associated with an increased synchrony in other brain regions. Liu et al. (2017) showed that a maintenance of delta and theta synchrony of central regions (measured with the PLI), in the absence of increased activity in other regions, was associated with decreased motor and cognitive performance. This suggests that maintenance is strongly linked to the presence of functional compensations. However, such increased brain activity could also be deleterious, reflecting network alteration and the presence of excitotoxic or neurodegenerative phenomena (Hillary and Grafman, 2017).

Non-Effective Changes

With advancing age, changes in brain function can be compensatory (as discussed above), but may also turn out to be ineffective. In an EEG study (Tóth et al., 2014), young and old healthy participants had to perform a working memory task consisting of remembering colored squares at certain locations. During the test phase, these squares remained at the same locations but could change in color. Participants had to determine whether squares were identical to those displayed during the encoding phase or not. Synchrony was determined with the PLI measure, and a specific decrease in theta synchrony between frontal and posterior sites was observed in healthy older adults compared to younger individuals (see also Li and Zhao, 2015). Importantly, this theta synchrony decrease has been associated with lower cognitive performance. Also, increased high gamma synchrony in the left frontal region during a maze task (visual planning task) has been shown to be negatively associated with performance (Paul et al., 2011).

In one of our studies (Jauny et al., 2022), we showed that maladaptive changes can be identified in resting-state activity. This study involved the Cam-CAN cohort (e.g., Shafto et al., 2014; Taylor et al., 2017) and changes in synchrony (with the PLV measure), as well as directed connectivity (with the entropy transfer measure, which provides a directed connectivity measure), were investigated. We observed a greater variability in brain networks' synchrony over time relative to younger individuals, mainly for the default mode network (this network is mainly activated when no task is proposed from the participant and plays a role in continuous environmental monitoring; Uddin et al., 2019) in the delta frequency band. Moreover, we showed that older individuals showed a revered dominant direction in information transfer, relative to younger individuals, with a significant increase in the anterior to posterior direction of functional connectivity. These changes were correlated with a decline in cognitive performance on tests measuring working memory, attention, and logical reasoning (also Sahoo et al., 2020). This reversal of the dominant information transfer direction could represent a failed compensation attempt. The increases in brain synchrony studied could also reflect excitotoxic processes (Hillary and Grafman, 2017; Mai et al., 2019), with increased activity preceding neuronal loss. Indeed, older individuals showing these hyperconnectivity phenomena had decreased cognitive performance.

As we have seen in these different sections, changes in synchrony vary over time and with task difficulty, and increased synchrony is not always beneficial. These changes appear to be related to changes in the level of white matter fibers integrity (Hinault et al., 2020, 2021). Indeed, the presence of white matter lesions has been associated with decreased brain synchrony (Wessel et al., 2016). In association with the influence of potentially preclinical excitotoxic processes, structural and functional changes could reflect the progression of neurodegenerative disorders.

PATHOLOGICAL AGING

In this section, we considered M/EEG study involving patients with AD and its prodromal stage called mild cognitive impairment. AD is the most common age-related pathology and is characterized by memory and cognitive control impairment (involving inhibition, planification, and mental flexibility; Baudic et al., 2006). The investigation of early AD stages such as the MCI stage is of significant interest because some individuals will later develop AD whereas others will remain stable or develop other pathologies such as frontotemporal or vascular dementia (e.g., Perez-Gonzalez et al., 2014; Jongsiriyanyong and Limpawattana, 2018). The reviewed studies were selected based on the same criteria as in the previous section on normal aging (see **Table 1**). The main results studied in this section are illustrated in **Figure 1B**.

Resilience

In line with the reserve concept developed in healthy older individuals, resilience refers to the processes involved in coping with the development of neurodegenerative disorders and the associated brain changes (Pascual-Leone and Bartres-Faz, 2021). Indeed, resilience allows, like reserve, the preservation of cognitive functions in spite of brain changes. Few studies have documented this phenomenon. Gaubert et al. (2019) compared resting-state EEG data (phase synchrony calculated using PLV and PLI) from patients with preclinical AD (at two AD progression stages) and control participants. They observed that the degree of neurodegeneration (measured by the level of amyloid beta load) impacted functional

TABLE 1 | Summary of the results.

References	Measure	Method	Task	Participants (age)	*N*	Results
				Healthy aging		
Compensation						
Ariza et al. (2015)	MEG	PLI	Working memory	Young healthy adults (21.88) Older healthy adults (64.45)	9 11	The global increase in alpha synchrony is positively correlated with the maintenance of cognitive performance in the elderly group
Aktürk et al. (2020)	EEG	Coherence	Facial expressions recognition task	Young healthy adults (24) Older healthy adults (62.07)	15 15	Increased delta, theta, and alpha synchrony in frontal position in healthy elderly would allow maintenance of cognitive performance compared to the young
Hong et al. (2016)	EEG	Phase synchronization analysis	Go/NoGo	Young healthy adults (21.4) Older healthy adults (61)	23 18	Increased delta and theta phase synchronization in the fronto-central and parieto-central areas is associated with the maintenance of cognitive performance for the elderly group
Phillips and Takeda (2010)	EEG	PLV	Visual search	Older healthy adults (68)	14	Increased gamma synchronization in the fronto-parietal position is positively correlated with cognitive performance in the elderly group
Rosjat et al. (2018)	EEG	PLV	Finger tap	Young healthy adults (22–35) Older healthy adults (60–78)	21 31	Maintenance of the increase in delta synchronization in the elderly (similar to the young group) could enable the maintenance of cognitive performance in this same group compared to the young group
Rosjat et al. (2021)	EEG	PLV	Finger tap	Young healthy adults (22–35) Older healthy adults (60–78)	21 31	Maintenance of the increase in delta and theta synchronization in the elderly (similar to that of the younger group) would allow the maintenance of cognitive performance
Maintenance						
Coquelet et al. (2017)	MEG	Power envelope correlation	Resting state	Young healthy adults (23.6) Older healthy adults (68.8)	25 25	Maintenance of synchrony in beta band in elderly at a similar level than the young group is positively correlated with cognitive performance
Hinault et al. (2020)	EEG	PLV	Working memory	Young healthy adults (23.2) Older healthy adults (71.0)	40 40	Older with preserved integrity of white matters fibers show preserved functional synchrony in alpha and gamma band and no difference in cognitive performance with younger participants
Ho et al. (2012)	EEG	Phase locking measures and coherence	Attention task	Young healthy adults (23.7) Older healthy adults (70.1)	15 15	Decreased theta and alpha synchronization in the parietal region are positively correlated with cognitive performance in the elderly group (No difference in cognitive performance between groups)
Liu et al. (2017)	EEG	PLI	Finger tap	Young healthy adults (22–35) Older healthy adults (60–78)	18 24	Maintenance of delta and theta synchronization of central regions in the elderly group associated with poorer cognitive performance compared to the young group
López et al. (2014b)	MEG	PLV and PLI	Sternberg task	Older healthy adults high cognitive reserve (67.3) Older healthy adults low cognitive reserve (69.7)	9 12	The low reserve group shows an increase in theta (fronto-parietooccipital), alpha (fronto-temporo-occipital) and beta (parieto-fronto-temporo-occipital) connectivity would allow maintenance of cognitive performance compared to the high reserve group

(Continued)

TABLE 1 | Continued

References	Measure	Method	Task	Participants (age)	*N*	Results
Rondina et al. (2019)	MEG	Phase synchronization analysis	Spatial memory	Young healthy adults (24.8) Older healthy adults (65.9)	16 16	Increased theta synchrony in occipital regions and decreased theta synchrony in fronto-temporo-parietal regions in the elderly in a manner similar to the young group allows maintenance of cognitive performance for the older group
Non-effective changes						
Hinault et al. (2021)	M/EEG	PLV	Working memory	Young healthy adults (23) Older healthy adults (71)	40 40	Decreased structural integrity in the elderly group alters the stability of communications (alpha and gamma frequency bands) between brain regions compared to the young group
Jauny et al., 2022	MEG	PLV and TE	Resting state	Young healthy adults (26.5) Older healthy adults (64.5)	46 46	Increased variability of delta synchrony in the DMN network and reversal of information transfer in the anterior to posterior direction of functional connectivity with age correlates with decreased cognitive performance
Li and Zhao (2015)	EEG	PLV	Visual search	Young healthy adults (23.9) Older healthy adults (63.1)	13 13	Increased theta and alpha centro-frontal synchrony and decreased beta centro-parietal synchrony in the older group could explain the decreased cognitive performance compared to the younger group
Paul et al. (2011)	EEG	Phase synchrony	Maze test	Young healthy adults (24.6) Older healthy adults (58)	160 100	Increased gamma2 synchrony in left frontal areas correlated with decreased cognitive performance for the older group
Sahoo et al. (2020)	MEG	Coherence	Resting state	Young healthy adults (18–35) Older healthy adults (66–88)	126 216	The decrease in alpha synchrony correlates with the decrease in cognitive performance on the VSTM test
Tóth et al. (2014)	EEG	PLI	Working memory	Young healthy adults (21.1) Older healthy adults (65.8)	20 16	Decreased theta synchronization between frontal and posterior regions could explain the decreased cognitive performance in the older group
Wessel et al. (2016)	EEG	PLV	Cognitive control	Older healthy adults (62) Older adults with focal frontostriatal lesion of withe matter (62.42)	12 12	The lesion group shows a decrease of beta synchrony
				Pathological aging		
Resilience						
Bajo et al. (2010)	MEG	Synchronization Likelihood	Memory task	Older healthy adults (71.6) MCI patients (74.8)	19 22	Increased alpha, beta and gamma synchronization in MCI participants is associated to the preservation of cognitive performance compared to the healthy elderly group
Gaubert et al. (2019)	EEG	PLV	Resting state	Older healthy adults (75.62) preclinical AD patients (76.88)	175 25	Increased alpha synchrony in preclinical ADs with low amyloid levels would allow preserve of cognitive performance at a level similar to healthy elderly. Amyloid deposits could have a negative impact on the extracellular environment, preventing compensatory adjustments.

(Continued)

TABLE 1 | Continued

References	Measure	Method	Task	Participants (age)	*N*	Results
Rondina et al. (2019)	MEG	Phase synchronization analysis	Spatial memory	Young healthy adults (24.8) Older healthy adults (65.9)	16 16	Increased theta synchrony in occipital regions and decreased theta synchrony in fronto-temporo-parietal regions in the elderly in a manner similar to the young group allows maintenance of cognitive performance for the older group
López et al. (2014a)	MEG	PLV	Resting state and working memory	Older healthy adults (71.8) MCI patients (72.5)	32 38	An overall increase in theta synchrony was reported in the right fronto-occipital and parieto-temporal regions for the MCI group, as well as an increase in delta synchrony in the interhemispheric frontal regions. All this would allow the MCI group to have similar cognitive performance to the healthy elderly group
Resistance						
Knyazeva et al. (2013)	EEG	S estimator	Resting state	Older healthy adults (67.6) AD patients (68.7)	15 15	Increased synchrony in individuals with MCI was initially associated with preservation of brain and cognitive functioning, but may also be a sign of disease progression
López et al. (2014a)	MEG	PLV	Resting state and working memory	Older healthy adults (71.8) MCI patients (72.5)	32 38	An overall increase in theta synchrony was reported in the right fronto-occipital and parieto-temporal regions for the MCI group, as well as an increase in delta synchrony in the interhemispheric frontal regions. All this would allow the MCI group to have similar cognitive performance to the healthy elderly group
Maladaptive changes						
Caravaglios et al. (2018)	EEG	coherence	Resting state and omitted tone task	Older healthy adults (69.6) aMCI patients (68.1)	15 15	Increase in beta synchrony in aMCI patients correlated with poorer performance on various neuropsychological tests
Garn et al. (2015)	qEEG	Coherence	Resting state	AD patients (76) probable AD patients (75)	118 79	qEEG synchrony markers could predict AD severity
Houmani et al. (2018)	EEG	Bump model	Resting state	SCD participants (68.9) AD patients (81.6)	22 49	Discrimination of SCD and AD groups based on synchrony measures
Li et al. (2019)	EEG	PLI	Digit verbal span task	Older healthy adults (62.75) mild AD patients (72.5)	8 6	The decrease of connectivity in the alpha and beta frequency bands in frontal and parieto-temporal areas is correlated with impaired cognitive performance
Teipel et al. (2009)	EEG	Coherence	Resting state	Older healthy adults (67.0) aMCI patients (73.6)	20 16	The decrease of white matter integrity causes a decrease in alpha synchrony for aMCI participants

EEG, electroencephalography; MEG, magnetoencephalography; PLI, phase lag index; PLV, phase-locking value; TE, transfer entropy.

connectivity. Higher alpha functional connectivity in parieto-occipital sites was observed when amyloid load levels were low. This increase in alpha connectivity was interpreted as reflecting a compensatory phenomenon as patients showed normal cognitive performance (measured by the Free and Cued Selective Reminding Test, assessing episodic memory). In the presence of high amyloid loads, theta functional connectivity was decreased. It was suggested that amyloid deposits could negatively impact the extracellular environment, preventing compensatory adjustments. Moreover, Bajo et al. (2010) administered a memory task to healthy elderly MCI participants with similar performance levels than controls. They reported an increased interhemispheric gamma, beta, and alpha synchrony in MCI participants compared to controls. This increase in synchrony has been interpreted as reflecting compensatory adjustments in MCI individuals. The presence of interhemispheric activity is in line with the Hemispheric Asymmetry Reduction in Older (Cabeza et al., 2002) model. Finally, an overall increase in theta synchrony has been reported in fronto-occipital and right parietotemporal areas for MCI individuals during the performance of a mental arithmetic task, thus allowing the maintenance of cognitive performance (López et al., 2014a).

These resilience phenomena have been reported in patients with MCI, but may not always be necessary. Indeed, López et al. (2014b) showed that increases in synchrony were reduced in individuals with greater reserve.

Resistance

Resistance refers to the prevention of brain injury and damage before their occurrence (Pascual-Leone and Bartres-Faz, 2021). AD is characterized by advanced brain and cognitive impairments, being the results of years of neurodegenerative processes, and therefore resistance phenomenon can no longer be observed. However, investigating the earlier stages of this disease, López et al. (2014a) used a mental arithmetic task (mental subtraction) at two levels of difficulty (subtracting from one to one, being the easy level, and subtracting from three to three being the hard level). Patients with MCI and controls both showed similar cognitive performance. Furthermore, lower synchrony at rest and increased delta synchrony in frontal interhemispheric regions during task completion (measured with PLV) were similar across groups. Thus, there seems to be maintenance of certain brain functions in early AD stages. However, such maintenance of specific brain communications was associated with compensatory increases in synchrony in other brain regions in patients with MCI. The concept of resistance, alone, would therefore not allow the maintenance of cognitive performance in individuals at risk of developing a neurodegenerative disease. Furthermore, increased synchrony in individuals with MCI was initially associated with preservation of brain and cognitive functioning, but may also be a sign of disease progression (Knyazeva et al., 2013).

Maladaptive Changes

Despite the presence of maintained synchrony patterns and the ability of some individuals to compensate for disease-related brain damage, individuals with MCI also exhibit brain changes associated with impaired cognitive performance. For example, Caravaglios et al. (2018) showed that increases in beta synchrony in patients with MCI correlated with poorer performance on various neuropsychological tests (e.g., Trail Making Test, Rey Auditory Verbal Learning Test, and Semantic Verbal Fluency). Maladaptive changes thus occur and could be due to disturbances in the integrity of white matter fibers. Altered white matter integrity has indeed been shown to result in decreased alpha synchrony in individuals with MCI, particularly in parietal regions (Teipel et al., 2009). Synchrony analyses have also revealed decreased connectivity in frontal and parietotemporal alpha and beta activity, especially in interhemispheric couplings, associated with impaired cognitive performance (digit verbal span task; Li et al., 2019).

Thus, maladaptive changes appear to differ depending on AD progression level. Garn et al. (2015) revealed that qEEG markers such as decreased delta synchrony in parietal regions could have a predictive role in AD severity. Indeed, synchrony measures could discriminate between individuals with subjective cognitive decline (SCD; defined by a subjective complaint without cognitive impairment), MCI, and AD (Houmani et al., 2018). Using measures of synchrony (bump model) and complexity (epoch-based entropy), the authors discriminated patients with AD from patients with SCD and high specificity (91.6% accuracy, 100% specificity, and 87.8% sensitivity). Their results showed that patients with AD showed increased EEG synchrony in the theta band in frontal and occipital regions compared to patients with SCD. These differences could be explained by the degradation or lower cognitive reserve in patients with AD (Montemurro et al., 2021).

DISCUSSION

Results reviewed here highlight the importance of considering the temporal dynamics of brain activity, and synchronized brain communications, to our understanding of cognitive reserve, resilience, and maintenance in healthy and pathological aging. Dynamic connectivity patterns must display both stability and flexibility as a function of the cognitive process involved and task context. While the stability of dynamics in the network engaged is important to process relevant information, flexibility is required to adjust to goal changes and to inhibit the processing of irrelevant information (e.g., Voytek and Knight, 2015). Cognitive decline during healthy and pathological aging can result from impairments of such dynamic network activity. While further investigations remain necessary, the present review summarizes current work on the association of sustained, increased, or altered neural synchrony across brain regions, with cognitive preservation or decline.

While reserve has been associated with increased frontal synchrony in the theta and alpha bands (Ariza et al., 2015; Hong et al., 2016), resilience has been associated with increased alpha, beta, and gamma synchrony (e.g., Bajo et al., 2010). It is important to note that not all changes are associated with a relative preservation of cognitive performance. Indeed,

maladaptive changes have also been reported, such as the increased delta synchrony in posterior regions (Jauny et al., 2022). Findings suggest that (1) the neural mechanisms involved in both reserve and resilience could be partly similar, and (2) resilience could involve a stronger involvement of higher frequency bands relative to reserve. This difference could be determined by the degree of preservation of the structural network integrity, which is modulated by the pathology progression, leading to different compensation levels. Yet, whether differences across reserve and resilience are mainly of quantitative nature, or also qualitative, remains to be further clarified.

Maintenance-related patterns were also observed in healthy older individuals, with a relative absence of impairments in frontoparietal communication dynamics associated with preserved cognitive performance (Rondina et al., 2019; Hinault et al., 2020, 2021). The brain's structure-function interplay appears to be at the heart of the heterogeneity associated with maintenance during aging (Courtney and Hinault, 2021; Jauny et al., 2022). Indeed, maintenance was observed with preserved dynamics in the relative absence of integrity loss. Conversely, reserve-related adjustments are a necessity in the presence of reduced structural integrity. The inability of any of these two mechanisms will lead to cognitive decline. Additional longitudinal studies remain necessary to further specify the concepts of maintenance and resistance mechanisms. Another open question for future research lies in the distinction between hyperactivation or hyperconnectivity resulting from (1) failed compensatory attempts, although some degree of network reorganization has been implemented, and (2) excitotoxic processes associated with the progression of neurodegenerative disorders. Direct investigations, associated with longitudinal follow-up, will be necessary to further clarify this distinction.

While these findings are promising, they only reflect a fraction of M/EEG aging studies. Future studies in the field could integrate the following recommendations to further address the contribution of brain dynamics. First, while resting-state measurements are indicators of the potential for brain networks' reorganization in cognitively challenging situations, they cannot always inform on their actual implementation and association with specific cognitive processes. Although few studies were conducted to address these issues, we expect that dynamic stability and flexibility of task-related networks could provide critical elements regarding subsequent cognitive changes and the effect of cognitive stimulation programs. In line with recent questioning in the field (e.g., Finn and Bandettini, 2021), it also appears critical to question whether resting-state recording can precisely measure elements of cognitive reserve. Although changes can be observed in brain activity at rest, specific task-related delays in the implementation, maintenance, or interruption of communications across brain regions could be highly sensitive to age and pathology effects. Recent work (Babiloni et al., 2020; Güntekin et al., 2021) highlighted the clinical value of investigating oddball-related brain activity to detect pathology effects. Finally, from an epidemiological perspective, future studies should also consider middle-aged individuals (40–60 years) to clarify the association between changes in brain dynamics and later cognitive trajectories. Indeed, age-related brain changes occur throughout life and changes in older individuals (>65 years) may be the result of earlier brain changes. Also, it appears critical that future studies include a more diverse population, especially in terms of education level (de Oliveira et al., 2018; Ashby-Mitchell et al., 2020). Indeed, most of the reviewed studies considered populations with a high level of education, which limits the investigation of reserve and resilience mechanisms.

Many studies relied on methods that are blind to temporal changes, such as amplitude comparison following averaging of large time periods. This facilitates data analyses but could lead to missing important information. Hidden-Markov models (Tibon et al., 2021) or multiscale entropy (McIntosh et al., 2014) enable the specification of time-varying connectivity states, which could further our understanding of the heterogeneity of cognitive aging. Finally, the majority of the reviewed studies involved sensor-based analyses and brain connectivity methods, such as coherence analyses. While the reviewed work reveals important patterns associated with resilience and maintenance, they are prone to volume conduction effects (e.g., Brunner et al., 2016) and suffer from low spatial accuracy. A more generalized use of non-biased connectivity estimates (e.g., Allouch et al., 2022), associated with source reconstruction of M/EEG activity, could clarify some open questions and replicate the currently reported findings. This would also enable the investigation of the same networks and regions of interest as previous fMRI work (Pascual-Leone and Bartres-Faz, 2021) to specify their time course and dynamics.

Brain connectivity changes observed in M/EEG could differentiate individuals according to pathology stages (Houmani et al., 2018) in a non-invasive manner. These data could also help predict pathology progression. Specifying rhythmic brain communication changes with age and pathology could also guide direct modulations of brain rhythms through targeted stimulations. Recent work, such as Reinhart and Nguyen (2019), revealed the feasibility of short-term interventions using transcranial alternative current stimulation (application of a low-intensity current to the brain with electrodes to synchronize or desynchronize brain oscillations) on working memory performance in healthy older adults. Improved working memory performance (up to 50 min post-stimulation) has been reported in healthy older adults following frontotemporal theta stimulation relative to a sham condition. Several points, such as the long-term benefits of these interventions, together with the optimal number of sessions, remain to be specified. Such knowledge could lead to a new specific and neurophysiologically grounded intervention targeting disrupted brain communications and enhancing rhythms associated with successful compensation, suggesting an intense development of this research field in the coming years.

AUTHOR CONTRIBUTIONS

GJ: investigation and writing. FE: supervision and review. TH: conceptualization, supervision, writing, and review. All authors contributed to the article and approved the submitted version.

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Age-Specific Activation Patterns and Inter-Subject Similarity During Verbal Working Memory Maintenance and Cognitive Reserve

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Cognitive Reserve (CR), according to a recent consensus definition of the NIH-funded Reserve and Resilience collaboratory,[1] is constituted by any mechanism contributing to cognitive performance beyond, or interacting with, brain structure in the widest sense. To identity multivariate activation patterns fulfilling this postulate, we investigated a verbal Sternberg fMRI task and imaged 181 people with age coverage in the ranges 20–30 (44 participants) and 55–70 (137 participants). Beyond task performance, participants were characterized in terms of demographics, and neuropsychological assessments of vocabulary, episodic memory, perceptual speed, and abstract fluid reasoning. Participants studied an array of either one, three, or six upper-case letters for 3 s (=encoding phase), then a blank fixation screen was presented for 7 s (=maintenance phase), to be probed with a lower-case letter to which they responded with a differential button press whether the letter was part of the studied array or not (=retrieval phase). We focused on identifying maintenance-related activation patterns showing memory load increases in pattern score on an individual participant level for both age groups. We found such a pattern that increased with memory load for all but one person in the young participants ($p < 0.001$), and such a pattern for all participants in the older group ($p < 0.001$). Both patterns showed broad topographic similarities; however, relationships to task performance and neuropsychological characteristics were markedly different and point to individual differences in Cognitive Reserve. Beyond the derivation of group-level activation patterns, we also investigated the inter-subject spatial similarity of individual working memory rehearsal patterns in the older participants' group as a function of neuropsychological and task performance, education, and mean cortical thickness. Higher task accuracy and neuropsychological function was reliably associated with higher inter-subject similarity of individual-level activation patterns in older participants.

Keywords: cognitive reserve, fMRI, multivariate analysis, verbal working memory, inter-subject similarity

[1]https://reserveandresilience.com/

INTRODUCTION

The objective of the current study was to use the well-studied letter Working-Memory Sternberg task (Braver et al., 1997; Cohen et al., 1997; Jonides et al., 1997; Manoach et al., 1997; Smith and Jonides, 1997, 1998; Smith et al., 1998; D'Esposito et al., 1999, 2000; Postle and D'Esposito, 1999; Rypma et al., 1999, 2001, 2002; Rypma and D'Esposito, 1999, 2000, 2003; Postle et al., 2000a,b) to investigate the associated activation patterns as possible mechanism of Cognitive Reserve (CR). Cognitive Reserve and its contributions to, and inputs from, working memory has been the focus of numerous investigations to date. When considering this body of work, it is important to keep in mind the conceptual definition of Cognitive Reserve, recently clarified in the framework of the NIH-funded "Reserve and Resilience" collaboratory.[2] The framework postulates that CR is a property or mechanism that explains cognitive performance beyond brain developmental changes and pathology, and literally reads "CR is a property of the brain that allows for cognitive performance that is better than expected given the degree of life course-related brain changes and brain injury or disease." Cognitive Reserve is thus a *relational* construct, whose ascertainment is impossible without a cognitive endpoint and a measure that captures at least one aspect of brain health or pathology. Colloquially speaking, CR encompasses mechanisms that explain cognitive performance *beyond the influence of brain status*. In the face of this updated definition, most of the Cognitive Reserve studies to date are wanting and present a significant knowledge gap in the extant literature.

There have been numerous studies linking Cognitive Reserve to working memory. In keeping with the definition introduced before, when no brain imaging is present to quantify brain health, such studies necessarily only deal with CR *proxies*, like, for instance, education, leisure activities, occupational attainment, reading ability etc. Such factors, discussed in a recent systematic review (Song et al., 2022), *might* indeed constitute Cognitive Reserve in the sense of the framework's stricter definition introduced above, but they cannot isolate the mediating mechanism of Cognitive Reserve conclusively beyond brain structural confounds. Superior brain health resulting in better cognition does not strictly qualify as CR and can happen in an orthogonal manner (Habeck et al., 2017). For the proper ascertainment of the presence and nature of CR, the recording of brain structural information is thus crucial but has rarely been undertaken, presenting a large gap in the field (See extensive literature review in the Discussion section.).

Since the most proximate cause of cognitive performance, and thus the obvious implementation of Cognitive Reserve, is the underlying brain activation, we wanted to repeat an age-specific derivation of load-related activation pattern, using the analytic framework in some of our earlier work in fMRI studies of verbal and non-verbal WM (Habeck et al., 2004, 2005b, 2012). We focused on the spatial activation patterns underlying the maintenance of verbal material. In contrast to our earlier work, age was considered explicitly in the analysis by looking at separate age groups, and relations between pattern scores, age, task performance, and general cognitive functioning were probed after derivation of the load-related maintenance pattern within each group.

We then wanted to test whether these activation patterns fulfilled the postulates of strict tenets of CR(Stern, 2002, 2009; Stern et al., 2019, 2020; Stern and Barulli, 2019). Since task performance was not used in the pattern derivation, the relationship of pattern utilization to task performance was likewise unconstrained. Pattern utilization could either display a positive or negative relationship with performance, or none. Significant relationships of the load-related maintenance pattern with task performance, beyond that accounted for by brain structure, would qualify as a manifestation of Cognitive Reserve. A negative sign of the relationship would indicate higher efficiency and indicate that better performing participants increase the load-related utilization of the pattern to a lesser degree than poorer performers. A positive sign, on the other hand, would indicate higher capacity in the better performers. Bivariate relationships with neuropsychological performance with the same sign as the relationship to task performance would likewise strengthen the CR interpretation.

Lastly, we were interested in widening our focus and considered the similarity of subject-level activation maps as a function of age, mean cortical thickness, task, and neuropsychological performance, without conducting any group-level pattern derivation. Beforehand, we had no expectation whether higher similarity (=lower inter-individual variability) of activation maps was associated with poorer or better performance or brain health. If conforming to a group-specific "template" is beneficial for performance, we might expect that better performing participants show higher inter-subject similarity. On the other hand, it is also conceivable, particularly for crystallized abilities, those individual neural strategies and their corresponding activation maps have been honed over a lifetime by high performers, and that consequently *lesser* inter-subject similarity might be expected. We investigated these possibilities by rigorous comparison of inter-subject similarities as a function of a variety of performance measures, age, education, and mean cortical thickness. Higher similarity can be seen as better robustness and lower variability of the topographic composition of the load-related patterns. *A priori* it was not clear whether such higher similarity would be associated positively or negatively with cognitive performance, brain structure, or younger age.

We summarize the addressable knowledge gap and its motivation for the current study: Cognitive Reserve has not been probed rigorously (i.e., comporting with the requirements of the recently funded NIH collaboratory about Reserve and Resilience) for working memory studies, and many studies have looked at the influence of *proxies*, rather than isolating mechanisms which influence cognitive performance beyond brain structural covariates. One obvious proximate mechanism that fulfills the strict Cognitive Reserve requirements would be task-related activation patterns whose pattern scores account for cognitive performance beyond brain structural variables.

[2]https://reserveandresilience.com/framework/

TABLE 1 | Subject sample characteristics.

	Younger group	Older group	Younger ≠ Older group?
Age (mean ± STD in years)	26.0 ± 2.9	**64.8 ± 3.2**	$p(t\text{-test}) < 0.0001$
Education (mean ± STD in years)	15.7 ± 1.9	16.1 ± 2.4	$p(t\text{-test}) = 0.11$
NART-IQ (mean ± STD)	114.3 ± 7.5	**118.3 ± 8.7**	$p(t\text{-test}) = 0.0058$
Mean cortical thickness (mean ± STD in mm)	**2.64 ± 0.11**	2.50 ± 0.11	$p(t\text{-test}) < 0.0001$
Sex (#Women, #Men)	31 W, 13 M	77 W, 60 M	p(Fisher exact) = 0.11

Bold values indicate a statistically significant difference between age groups at $p < 0.05$.

We aimed to test for the presence of such patterns and probe their association with traditional CR proxies, like education.

MATERIALS AND METHODS

Participant Sample and Demographics

Analyses included data from 181 strongly right-handed, native English-speaking healthy adults. Participants were recruited *via* random market mailing and screened for MRI contraindications and hearing or visual impairment that would impede testing. Older adult participants were additionally screened to eliminate those with dementia or mild cognitive impairment. Other exclusion criteria included: myocardial Infarction, congestive heart failure or any other heart disease, and brain disorder, such as stroke, tumor, infection, epilepsy, multiple sclerosis, degenerative diseases, head injury (loss of consciousness > 5 min), intellectual disability, seizure, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, essential/familial tremor, Down Syndrome, HIV Infection or AIDS diagnosis, learning disability/dyslexia, ADHD or ADD, uncontrolled hypertension, uncontrolled diabetes mellitus, uncontrolled thyroid or other endocrine disease, uncorrectable vision, color blindness, uncorrectable hearing and implant, any medication targeting central nervous system, cancer within last 5 years, renal insufficiency, untreated neurosyphilis, any alcohol and drug abuse within last 12 month, recent non-skin neoplastic disease or melanoma, active hepatic disease, insulin dependent diabetes, any history of psychosis or ECT, recent (past 5 years) major depressive, bipolar, or anxiety disorder, objective cognitive impairment (dementia rating scale of <130), and subjective functional impairment (BFAS > 1). A complete description of the participants in terms of demographics and cortical thickness can be found in **Table 1**.

Neuropsychological Assessment

All participants completed a standardized battery of neuropsychological assessments, and tasks were administered in the following order: Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997), Letter-Number Sequencing, American National Adult Reading Test (AMNART; Wechsler, 1997), Selective Reminding Task (SRT) immediate recall (Buschke and Fuld, 1974), WAIS-III Matrix Reasoning (Wechsler, 1997), SRT delayed recall and delayed recognition (Buschke and Fuld, 1974), WAIS-III Digit Symbol (Wechsler, 1997), Trail-Making Test versions A and B (TMT-A/B; Reitan, 1978), Controlled Word Association (C-F-L) and Category Fluency (animals; Benton et al., 1983), Stroop Color Word Test (Golden, 1975), Wechsler Test of Adult Reading (WTAR; Holdnack, 2001), WAIS-III Vocabulary (Wechsler, 1997), and WAIS-III Block Design (Wechsler, 1997). Based on a prior analysis in our lab assessing the factor structure of these tasks, four domain scores were generated by *z*-scoring all tests relative to the full baseline sample, and averaging task *z*-scores within each domain: Episodic Memory (all SRT outcomes), Vocabulary (WAIS Vocabulary, WTAR, and AMNART), Processing Speed (WAIS Digit Symbol, Stroop Color, Stroop Color Word, and TMT-A), and Fluid Reasoning (WAIS Matrix Reasoning, WAIS Block Design, and TMT-B). The primary outcome measures used in the present study included the domain *z*-scores for all four cognitive domains. A further average of these four scores was performed to yield a score for total cognition (=G).

MRI Data Acquisition

A high-resolution structural and fMRI BOLD images of the human brain were acquired in an event-related design using a 3.0 T Philips Achieva Magnet with standard quadrature head coil.

Structural MRI Acquisition and Processing

Each participant's structural T1 scans were reconstructed using FreeSurfer v5.1.[3] The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation (Fischl et al., 2002, 2004) has been reported to be comparable to manual labeling. Each participant's white and gray matter boundaries, as well as gray matter and cerebral spinal fluid boundaries, were visually inspected slice by slice, and manual control points were added in case of any visible discrepancy. Boundary reconstruction was repeated until satisfactory results for every participant were reached. The subcortical structure borders were plotted by TkMedit visualization tools and compared against the actual brain regions. In case of discrepancy, they were corrected manually. We took the mean cortical thickness measures reported for both hemispheres and averaged them, to arrive at one global measure per participant.

fMRI Acquisition of the Sternberg Working Memory Task

Functional data were acquired in three runs, each of which included collection of 314 functional volumes using a T2*-weighted gradient-echo echo planar image sequence. About 36 transverse slices per volume with 3.0 mm thickness and no gap in between were acquired using a field echo echo planar imaging (FE–EPI) sequence with the following parameters: TR 2,000 ms, TE 20 ms, and flip angle 72; in-plane acquisition matrix 112 × 112 matrix; which results in a voxel size 2.0 mm × 2.0 mm × 3.0 mm.

[3]http://surfer.nmr.mgh.harvard.edu/

Task stimuli were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Participants viewed the screen *via* a mirror system located in the head coil and, if needed, had vision corrected to normal using MR compatible glasses (manufactured by SafeVision, LLC. Webster Groves, MO, United States). Task administration and collection of behavioral data were conducted using PsyScope 5X B53 (Macwhinney et al., 1997). Task onset was electronically synchronized with the MRI acquisition computer.

Letter Sternberg task

Participants studied an array of either one, three, or six upper-case letters for 3 s (=encoding phase), then a fixation screen was presented for 7 s (=maintenance phase), to be probed with a lower-case letter, presented for 3 s. Participants were told to respond as quickly as possible with a differential button press whether the letter was part of the studied array or not (=retrieval phase). The probe letter remained on screen for the full 3 s regardless of response time. For the current study, we only focused on the maintenance phase.

Sternberg Task fMRI Data Processing

Subject-Level Pre-processing

FMRIB Software Library v5.0 (FSL) and custom-written Python code were used to perform the following pre-processing steps for each participant's dataset: All functional images were realigned to the first volume, corrected for the order of slice acquisition, smoothed with a 5 mm^3 non-linear kernel followed by intensity normalization, and high-pass filtered using a Gaussian kernel and cutoff frequency of 0.008 Hz. For spatial normalization, the accompanying T1-weighted high-resolution anatomic image was co-registered to the first functional volume using the mutual information co-registration algorithm implemented in FLIRT. This co-registered high-resolution image was then registered to MNI standardized space. These obtained transformation parameters were used to transfer the statistical parametric maps of the subject-level analysis to standard space.

The fMRI time series data were pre-whitened to explicitly correct for intrinsic autocorrelations in the data. The FEAT module (Woolrich et al., 2001) in FSL was used for first-level analysis. An event-related design was used to model the fMRI data, allowing us to separate timeouts (where no response was made), correct and incorrect trials, task loads (Braver et al., 1997; Jonides et al., 1997; Smith and Jonides, 1998), and task phases (encoding, maintenance, and retrieval). Incorrect responses and timeouts were modeled together. For all participants, a first-level analysis was run on each of their task-based runs with nine regressors: 3 task loads × 3 task phases. The regressors were generated by convolving FSL's double gamma canonical HRF with the duration of the respective task phases: encoding = 3 s, maintenance = 7 s, and retrieval = RT. A second level analysis was run on each participant by combining the first-level contrasts for each run. Contrasts for the retention phase of the three memory loads, 1, 3, and 6, were used in subsequent analysis.

Ordinal Trend Canonical Variates Analysis and Brain-Behavioral Analysis

We first identified a memory load-related activation pattern during the retention (=maintenance) period. We applied Ordinal Trend Canonical Variates (OrT-CVA) analysis (Habeck et al., 2004, 2005a) to derive a group-level activation pattern that shows an increase in pattern expression during the retention period with memory load on an individual subject level. We can write the multivariate decomposition achieved by OrT-CVA as follows. The derived activation pattern will be written as v, and participant S's activation map for memory load L can be written as the indexed column vector $y(S,L)$. This activation map can be written as the product of the group-level activation pattern with a subject- and load-dependent factor score w(S,L) and some unaccounted residual ε:

$$y(S,L) = w(S,L)\,v + \varepsilon$$

Ordinal Trend Canonical Variates puts constraints on the factor score $w(S,L)$ and derives an activation pattern whose factor score shows a positive within-person relationship with memory load for as many participants as possible, with an inferential framework for ascertaining significance through a permutation test.

For the estimation of topographic robustness, a bootstrap estimation procedure was conducted which resampled all participants and performed the OrT-CVA point estimate procedure on the resampled data 500 times. A topographic Z-map was approximated semi-parametrically by computing the bootstrap variability as a SD around the point estimate, and dividing the point estimate by this SD as.

$$Z(\text{voxel}) = \text{point estimate loading}(\text{voxel}) / \text{STD}(\text{voxel})$$

A minimum value of $|Z| > 2$ is required for regions to be highlighted with a consistent loading in a visualization plot. We performed a bootstrap procedure with 500 iterations and resampled the data with replacement, repeating the complete OrT-CVA analytic stream to compute Z-maps quantifying the robustness of each voxel's contribution to the covariance pattern. In addition to the group-specific robustness Z-maps, we also computed all possible $500 \times 500 = 250{,}000$ difference maps and looked at the voxels which lay in the 95% tail of the difference distribution, flagging significant differences in the loadings between young and old participants.

Relationship Between Regional Cortical Thickness and Sternberg Task Performance

We performed region-wise univariate analysis and related cortical thickness to Sternberg task performance in both age groups separately and identified a set of regions whose thickness shows

a negative association with load-averaged reaction time, and a set of regions whose thickness shows a positive association with load-averaged accuracy. We used a liberal threshold of $p < 0.05$, and then combined all identified regions with this liberal screen into one linear combination through linear regression analysis. In the end, we thus ended up with four thickness-based estimates of task performance for two outcomes and in two age groups. These thickness-based performance estimates where used in any subsequent brain-behavioral analysis involving the derived load-related activation pattern, to maximize the variance accounted for in the task performance variables by cortical thickness.

Inter-Pattern Similarity in the Older Group as a Function of Performance, Education, and Mean Cortical Thickness

In the next section, we tried to address the question whether age or education causes smaller or larger inter-individual variability, and whether or how good cognitive performance or preserved brain structure can offset any differences of activation patterns between individuals. For age, education, and cortical thickness, we just performed a median split of the older participants. For neuropsychological and task performance, to adjust for confounding factors, we residualized these measures regarding age, education, sex, and cortical thickness performance estimate, and then split the residuals along the respective median. Both procedures resulted in an assignment of each older participant into a "high" and "low" group with respect to each variable of interest. Our question was whether inter-individual similarity in activation maps differed between the "high" and "low" group, that is, we wanted to test the null-hypothesis:

$$R_{\text{high}}(k,j) = R_{\text{low}}(m,n)$$

For all subject pairs, (k,j) in "high" and (m,n) in "low"

For this test, we computed all possible $N^*(N\text{-}1)/2$ pairwise inter-subject spatial correlation coefficients (where N is 68 and 69, respectively). These inter-spatial correlation coefficients can be contrasted with a simple t-test for a point estimate computation; however, to assess statistical significance, a permutation test is needed that repeats the inter-subject similarity computation for null conditions. That is, we permuted participants randomly between "high" and "low" groups, creating null conditions, and repeating the within-group inter-subject similarity computation and the computation of the group comparison T-statistic. This was done 1,000 times to create a null-histogram, and statistical significance was approximated with a two-tailed test as $P(|T(\text{permutation})| > |T(\text{point estimate})|)$. This procedure is necessary since a parametric test would overestimate the number of the degrees of freedom and the T-statistic itself, and consequently suffer from value of p inflation with nominal value of p that would be too small.

RESULTS

We identified reliable load-related patterns during the retention phase in both age groups. In the younger participants, a best-fitting load-related pattern was constructed from PCs 1–21 and one of the participants did not conform to the majority rule of positive expression slopes ($p < 0.001$, permutation test). In the older participants, we constructed a pattern from PCs 1–45, and nobody deviated from the majority positive-slope rule ($p < 0.001$, permutation test). **Figure 1** shows the task–activity curve for every participant in both age groups.

The OrT-CVA technique imposes no *a priori* relationship between load-related slopes and load averages of pattern scores, and any relationship (negative, positive, or no correlation) is conceivable *a priori*, which we verified the correctness of parametric assumptions with permutation tests. For both groups, the load-related pattern score slope was positively correlated with the mean pattern score (Young: $R = 0.4143$, $p = 0.0052$; Old: $R = 0.5048$, $p < 0.0001$). Participants manifesting higher pattern score slopes thus also showed higher overall pattern scores. This finding refuted possible ceiling effects, with task–activity curves starting at relatively high levels with consequently lesser load increases.

We related the load average and slope of the pattern expression scores to Sternberg task performance (load average and slope of accuracy and reaction time) and four domains of neuropsychological functioning in bivariate correlations and found notably different brain-behavioral correlations as a function of age. We only report significant correlations: in the younger group, the pattern expression slope correlated negatively with mean load-averaged task accuracy in the Sternberg task ($R = -0.32531$, $p = 0.031183$), fluid reasoning ($R = -0.37756$, $p = 0.011516$), and vocabulary ($R = -0.39524$, $p = 0.0079228$). In the older group, pattern slope correlated positively with mean Sternberg task accuracy ($R = 0.17672$, $p = 0.038851$), and the mean pattern score correlated positively with mean Sternberg task accuracy ($R = 0.28577$, $p = 0.00071152$), perceptual speed ($R = 0.21227$, $p = 0.012767$), and vocabulary ($R = 0.21027$, $p = 0.013655$).

We performed a bootstrap procedure and computed Z-maps quantifying the robustness of each voxel's contribution to the covariance pattern, as well as inferential difference maps identifying old–young differences with 95% confidence. The results are shown in **Figure 2**. Topographic composition of both patterns shared a lot of similarities but involved two stark differences showing additional involvement of areas in the older participants: the involvement of the posterior cingulate for negative loadings and bilateral precuneus for positive loadings (**Supplementary Table 3**).

Super-threshold regions for all three images with anatomical annotation are listed in **Supplementary Tables 1–3**.

We also related regional cortical thickness to load-averaged reaction time and accuracy in both age groups, see **Table 2**.

Apart from bivariate correlations, we also ran linear regressions to predict load-averaged Sternberg accuracy rates with pattern scores, demographics, and the performance estimate based on

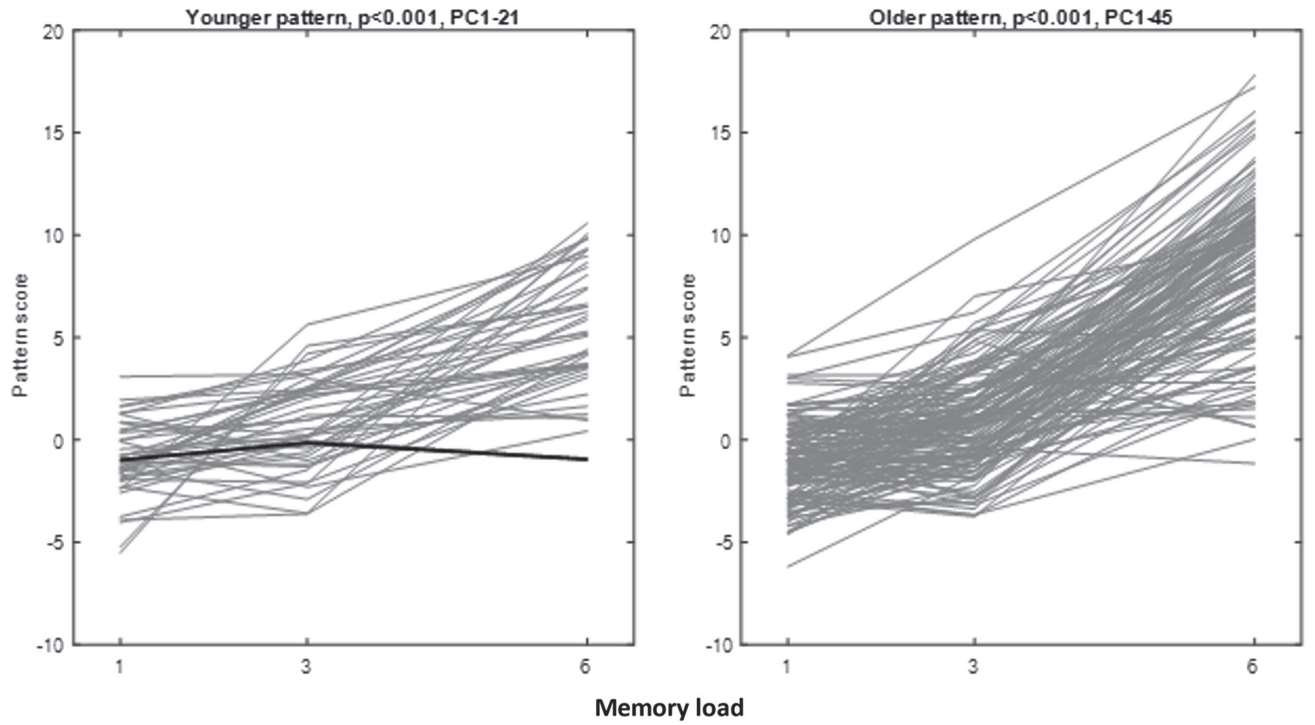

FIGURE 1 | Pattern score curves for the Ordinal Trend (OrT) patterns derived for younger and older participants. Exceptions to the positive-slope rule are shown in bold face. There was one exception in the young group, but none in the older group.

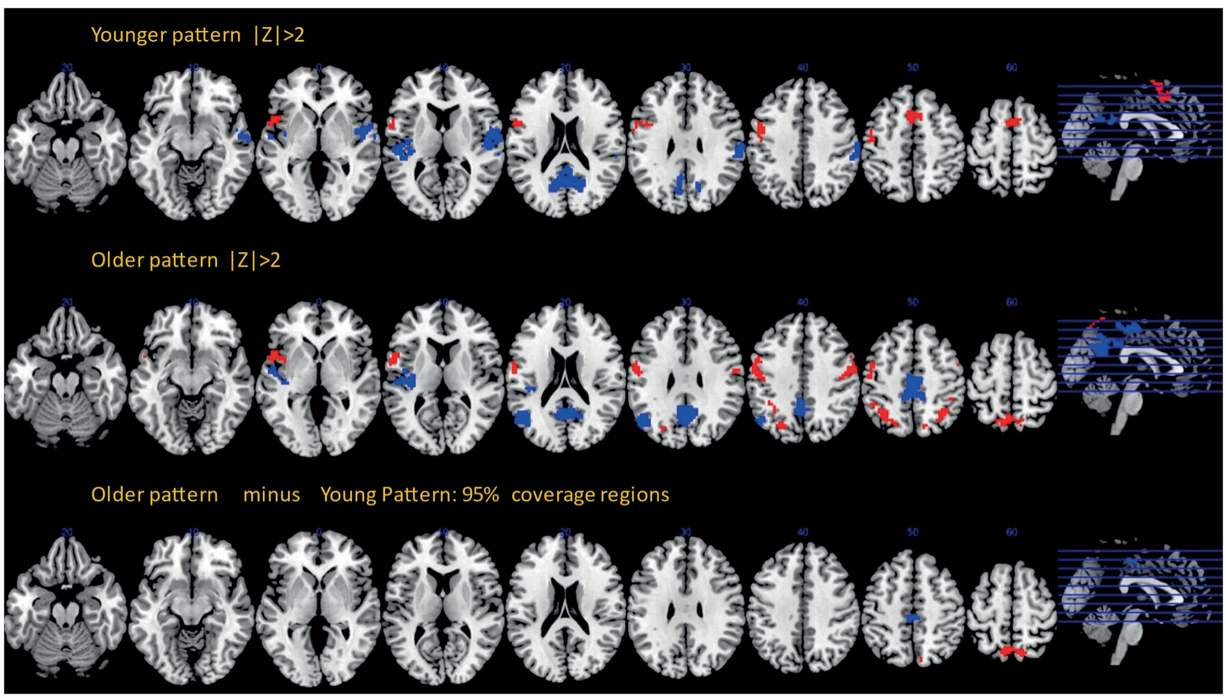

FIGURE 2 | Bootstrap *Z*-maps (top and middle rows) thresholded at $|Z|>2$, cluster size > 50. Bottom row: inferential comparison of old and young patterns, showing areas with the 95% coverage intervals excluding zero values.

TABLE 2 | Relationships between regional cortical thickness and task performance on Sternberg task.

Endpoint and age group	FreeSurfer label of associated regions at $p < 0.05$
Reaction time in younger group (negative association)	lh-isthmuscingulate, rh-medialorbitofrontal
Reaction time in older group (negative association)	lh-inferiortemporal, lh-medialorbitofrontal, lh-middletemporal, lh-parahippocampal, lh-precuneus, lh-temporalpole, lh-insula, rh-entorhinal, rh-fusiform, rh-inferiortemporal, rh-lateraloccipital, rh-lateralorbitofrontal, rh-middletemporal, rh-parahippocampal, rh-temporalpole, and rh-insula
Accuracy in younger group (positive association)	lh-paracentral, lh-postcentral, lh-precentral, lh-supramarginal, lh-transversetemporal, rh-inferiorparietal, rh-postcentral, and rh-transversetemporal
Accuracy in older group (positive association)	lh-isthmuscingulate, lh-posteriorcingulate, and rh-isthmuscingulate

TABLE 3 | Mean load-averaged task accuracy as a function of pattern-score mean levels and slopes, neuropsychological functioning, and demographics.

Outcome: mean task accuracy	Young		Old	
	T-statistic	*p* value	*T*-statistic	*p* value
Intercept	0.7531	0.4563	0.4838	0.6293
Mean pattern score	**2.2210**	**0.0327**	1.8505	0.0665
Pattern score slope	−1.4905	0.1448	1.0507	0.2954
Thickness-based accuracy estimate	**3.1379**	**0.0034**	**2.3689**	**0.0193**
Age	1.6710	0.1034	0.8319	0.4070
Total G	**2.4477**	**0.0194**	**3.5071**	**0.0061**
Education	−1.0555	0.2982	−0.3157	0.7527
Sex	0.5569	0.5810	−0.1460	0.8842

Pattern scores can account for task accuracy beyond the covariates with only marginal p value in the older participants. Total cognition (=G) account for performance beyond cortical thickness too. Bold values indicate a statistically significant difference between age groups at p < 0.05.

cortical thickness as covariates. **Table 3** below revealed the importance of general intelligence as measured by G since it contributed to task performance above all other measures. Only in the younger group did the mean pattern score of the load-related pattern also contribute to task performance; in the older group, significance of this association was only marginally significant with $p = 0.0665$ (We performed corresponding linear regressions to predict mean reaction time in both age groups but did not find any associations with the load-related patterns in either age group and elected to omit the table listing for clarity.).

We decided to run an *ad hoc* analysis and project the pattern derived in the younger group into the activation data of the older group to examine the degree that older adults express the younger adults' activation pattern. Multivariate patterns possess this convenient feature and enable simple cross-applications to *de novo* data. When computing bivariate correlations between subject variables with the obtained pattern scores like before, we found positive associations between the mean load-averaged pattern score and task performance ($R = 0.20946$, $p = 0.014029$) as well as perceptual speed ($R = 0.20802$, $p = 0.014719$).

Next, we turned to the dichotomization of the older group along several median splits based on task performance, neuropsychological functioning, education, and mean cortical thickness and observed the group differences in the inter-subject similarity of mean activation patterns. We found no significant differences between "high" and "low" groups for age, education (shown in **Figure 3**), mean cortical thickness, or task reaction time (minimum value of p for four comparisons from permutation test: 0.227). Significantly higher similarity was found for the "high" group for mean task accuracy ($T = 11.6054$, $p = 0.0070$, shown in **Figure 3**), memory ($T = 11.8313$, $p = 0.0060$), fluid reasoning ($T = 12.9849$, $p = 0.0008$), speed ($T = 9.7044$, $p = 0.0300$), and vocabulary ($T = 11.9092$, $p = 0.0090$).

Although it was only of secondary interest, we also performed several comparisons of inter-subject similarity involving the young participants, comparing all young and old participants. We found significantly higher inter-subject similarity for old compared to young adults ($T = 10.1118$, $p = 0.034$). When we revisited the median splits in the older participants, this difference was only found for the contrast of young adults vs. high-performing older adults. This hinted at inverted u-shaped behavior of inter-subject similarity regarding age-related performance: inter-subject similarity was low for young and low-performing older participants on the two ends, but high for high-performing older participants in the middle.

DISCUSSION

We identified load-related activation patterns during the maintenance phase of a verbal working memory task in two age groups that showed relationships to neuropsychological functioning and task performance, even though these relationships differed starkly as a function of age. In the young-participant group, the load-related increases, that is, the slope of pattern scores, related *negatively* to neuropsychological functioning and mean task accuracy, that is, poor performers increased their pattern score in response to memory load increases to a greater degree. Apparently, the younger participant's rehearsal pattern can be interpreted as *necessary*, but greater engagement of it in response to memory load was *not* conducive to good performance. In the older participant group, on the other hand, the load-related slope of pattern scores related positively to mean accuracy, as did the mean load-averaged pattern scores, which also correlated positively with neuropsychological functioning. Further, when prospectively applying the young-derived activation pattern into the older group's activation maps, the resulting mean load-averaged pattern scores still displayed positive correlations with mean task accuracy neuropsychological functioning (=perceptual speed). If the young-derived activation pattern can be considered as a "template," then higher manifestation of this template in the

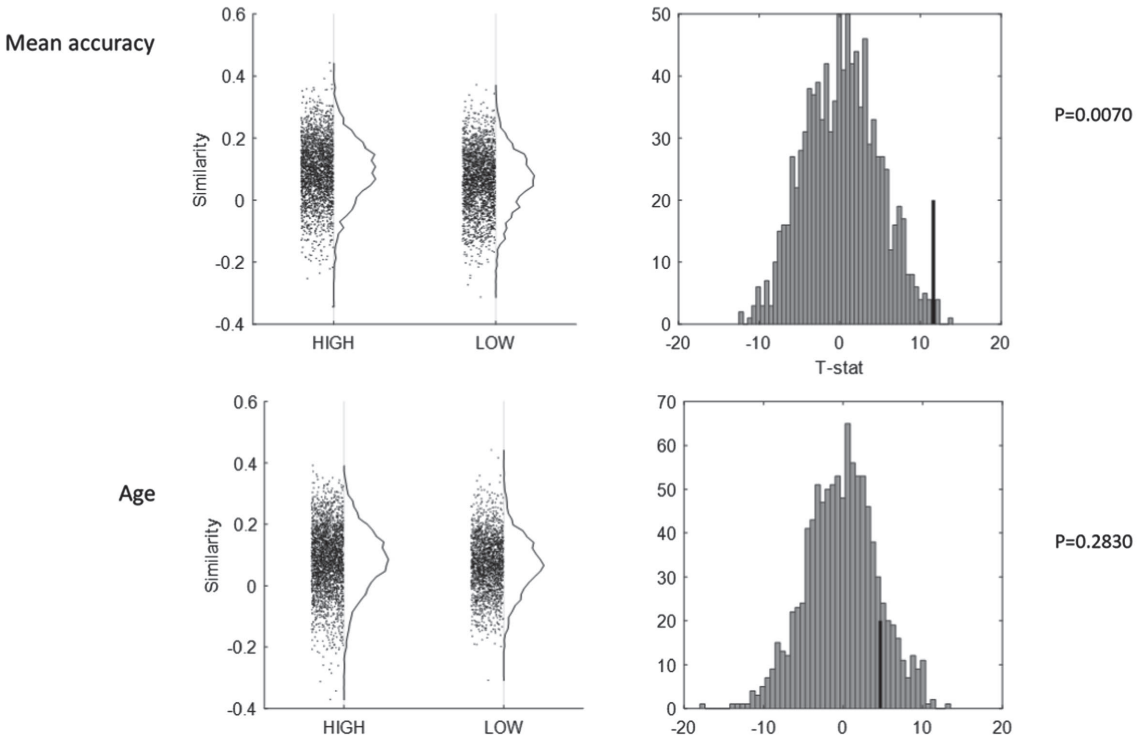

FIGURE 3 | Inter-subject pattern similarity as a function of mean task accuracy (top row), and age (bottom row). All inter-subject similarity values are plotted against HIGH and LOW status (left column), with null-histograms for the group contrast from a permutation test of 1,000 iterations (right column). The group with higher task accuracy showed higher inter-subject similarity ($p = 0.0070$), whereas age was non-differential ($p = 0.2830$).

older groups is associated with better task performance and better perceptual speed. The young activation pattern can be considered an implementation of Cognitive Reserve since load-averaged pattern scores accounted for task performance beyond cortical thickness, general cognition, and demographics; the activation pattern from the older group only achieved marginal significance in this regard. One caveat is that cortical thickness is only *one* possible measure of brain health and ideally a more holistic assessment which integrates several modalities, like gray matter volume and thickness, white-matter integrity, and absence of amyloid and tau protein accumulation, should be used.

Our study started to address a significant knowledge gap in the field. While there have been numerous studies invoking the concept of Cognitive Reserve, few of them comported with the strict definition of the recent clarification in the NIH-funded initiative "Reserve and Resilience."[4] Behavioral studies have demonstrated the link between working memory and general cognition in many different forms. Questionnaire-based operationalization of CR has shown correlations with working memory performance in patients with subject memory complaints (Lojo-Seoane et al., 2020), education has been shown to predict performance on an N-back task (Zarantonello et al., 2020), while vocabulary ability reduced working memory differences between participants with single- and multi-domain Mild Cognitive Impairment (Facal et al., 2014). In a community sample, verbal intelligence had stronger associations with working memory than education or socioeconomic status (Jefferson et al., 2011). For cognitive interventions, such as training on the N-back task, training-related improvements (Mičič et al., 2020) correlated with a measure operationalized through the Cognitive-Reserve Index questionnaire (Nucci et al., 2012). Working memory itself could be a form of Cognitive Reserve, as shown in a study (Sandry and Sumowski, 2014) that looked at intellectual enrichment and long-term memory outcomes in multiple sclerosis patients and found independent contributions by working memory capacity and, crucially, a moderation of the relationship between intellectual enrichment and long-term memory outcomes.

A different class of studies has related CR proxies to functional brain signals, without simultaneous consideration of brain structure or pathology. These studies often establish robust functional correlates of CR proxies, while still following short of the rigor required by the "Reserve and Resilience" framework. Event-related potentials (ERPs) recorded with electro-encephalography can link latency and amplitude of the signal to working memory performance or CR proxies with suggestive findings for increased efficiency with, for instance, reading ability (Gutiérrez-Zamora Velasco et al., 2021) or verbal intelligence and education (Speer and Soldan, 2015). While

[4]https://reserveandresilience.com/

these studies clearly demonstrate ERP correlates of CR proxies, a rigorous ascertainment of CR cannot be established because of the absence of brain structure or pathology measures. Even when such information is present, the full analyses required to decide about CR mechanisms are not always run. For instance, an fMRI study of a two-back task (Bartrés-Faz et al., 2009) showed correlations between fMRI activation and a composite of education, occupation, verbal ability, and leisure activities, supporting the notion of increased processing efficiency, but did not directly use the structural covariate of regional gray matter volume in a combined analysis. Similarly, in a recent fMRI lifespan study (Archer et al., 2018) of a spatial WM task where regional gray matter volume was used as a structural covariate, rigorous tests of Cognitive Reserve conforming to the framework's standards were lacking. The study showed negative associations between task-related activation and age in a monotonic fashion and thus substantiated age-related decreases in processing efficiency, although adjustments for education rendered some of these relationships non-significant. Crucially, the test of any contribution of education to task performance beyond the study's covariate of choice, *gray matter volume*, necessary to verify education's role as a Cognitive Reserve mechanisms, was also not conducted. Education was shown to be associated positively with task performance in bivariate correlations, but without the clarification of the role of gray matter volume, a clear differentiation between brain maintenance versus Cognitive Reserve effects, again, could not be made in the characterization of the education effect.

Other interesting studies that capture the spirit, if not the full operationalization, of the "Reserve and Resilience" framework can be found when the effect of general health impediments is not explicitly localized in the brain but can be shown to have a detrimental effect on working memory, with a moderation of the health-cognition relationship by CR proxies. In one study (Ihle et al., 2018), hypertension lowered working memory performance, but this effect was lessened when education, occupational demands, and leisure activities were considered too.

In conclusion, we can say studies that have investigated working memory and possible CR mechanisms with an adequate account brain structure or pathology are thus quite sparse in the extant literature. A recent study of the effect of bilingualism on performance of a two-back task (Anderson et al., 2021) showed structure–cognition associations that differed between bilinguals and monolinguals, which constitute a rigorous test of Cognitive Reserve consistent with the NIH-funded "Reserve and Resilience" framework. Similarly, after matching dyads of participants on hippocampal volume, one study showed that education was positively associated with working memory performance, among several cognitive outcomes (Rodriguez et al., 2019). Lastly, verbal intelligence has been shown to lessen the detrimental effect of amyloid deposition on working memory (Rentz et al., 2010).

After deriving task-related activation patterns and confirming their fulfillment of the Cognitive Reserve postulates, we also investigated the inter-subject similarity of load-averaged activation patterns underlying the maintenance phase as a function of age, task and neuropsychological performance, education, and mean cortical thickness. Younger adults had lower inter-subject similarity than older adults, hinting at a narrowing of individual neural strategies with age. In the older group however, *higher* inter-subject similarity was associated with *better* performance (but *not* longer education). Both young and low-performing older adults presented with lower inter-subject similarity than high-performing older adults.

This non-monotonic behavior of inter-subject similarity (=topographic robustness) was somewhat surprising. Inter-individual variability has not been researched extensively, and intra-individual variability has received the most of the field's recent attention (Armbruster-Genc et al., 2016; Nomi et al., 2017; Grady and Garrett, 2018; Pur et al., 2019; Roberts et al., 2020). Within a person and region, these studies broadly suggest that increased task demand and better cognitive performance might cause increased fMRI variability, and age might negatively impact cognitive performance *via* both depressed variability overall and the lower ability to increase variability in response to task demands. The implications of this research for inter-individual variability are not clear: inter-individual variability indicates that different people are employing different neural substrates, leading to lower inter-subject similarity. This reduced inter-subject variability can be seen as a group-level manifestation of a Cognitive Reserve mechanism: high performers seem to involve more similar individual-level activation maps than poorer performs. Since our findings are cross-sectional they can suggest plausibility, while longitudinal lifespan studies can more rigorously disentangle aging from age effects for any neural substrates, including inter-subject variability.

In summary, our study illustrated two facets of Cognitive Reserve and resilience in aging. We identified a memory load-related maintenance pattern that was positively associated with performance and neuropsychological functioning, but not with cortical thickness, in older participants. Interestingly, in younger participants, a topographically similar pattern could be identified, but the performance relations were strikingly different: higher deployment of the pattern in response to memory load was associated with *worse* performance on the task and *worse* neuropsychological functioning, hinting at a possible critical age range at which this change might occur, to be investigated more thoroughly in lifespan data with continuous age coverage. The different relations to performance notwithstanding, the pattern derived from young participants fulfilled the tenets of Cognitive Reserve and its mean load-averaged pattern scores were associated with task performance beyond brain structure, while the pattern derived from older participants achieved marginal significance. High inter-subject similarity of activation maps, which was assessed outside a group-level analytic framework, can be considered a form of (group-level) Cognitive Reserve as well, at least in the older participants, and is associated with more robust group-level activation patterns too. This suggests that better cognitive functioning might converge on *one* optimal neural strategy, deviations from which might be suboptimal in older age. An alternative scenario might be one of *neural flexibility* at the group-level, that is, a scenario where high-performing participants have honed their individual neural strategies and use *different* activation patterns from each

other, hampering an effective group-level analysis strategy. Covariance analysis in general can accommodate differences *in degree* along a group-invariant construct (=activation pattern) but cannot accommodate differences *in kind* very effectively. If high performers showed greater inter-subject variation in the topographic composition of their individual-level activation maps, tailoring a group-level pattern would involve an increased numbers of principal components, with correspondingly lower inferential robustness.

Such group-level variability with *positive* association to Cognitive Reserve might be conceivable for other cognitive tasks beyond working memory; investigation of inter-subject similarity and group-level robustness and its association with Cognitive Reserve, age and aging in longitudinal lifespan data will remain on our agenda for the near future.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Dryad Repository, final DOI: 10.5061/dryad.bzkh189c3. Preliminary access: https://datadryad.org/stash/share/gQSaYyiwz9he9_KI37ufnZpSLZU8VrzKAa8wMnYIdJU.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Protection Office and IRB, Columbia University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CH: conceptualization, analysis, and manuscript writing. YG: data pre-processing and manuscript writing and editing. YS: manuscript writing and editing and study design. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.852995/full#supplementary-material

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Age-Dependent Association Between Cognitive Reserve Proxy and Longitudinal White Matter Microstructure in Older Adults

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Objective: This study examined the association of lifetime experiences, measured by a cognitive reserve (CR) composite score composed of years of education, literacy, and vocabulary measures, to level and rate of change in white matter microstructure, as assessed by diffusion tensor imaging (DTI) measures. We also examined whether the relationship between the proxy CR composite score and white matter microstructure was modified by participant age, *APOE*-ε4 genetic status, and level of vascular risk.

Methods: A sample of 192 non-demented (n = 166 cognitively normal, n = 26 mild cognitive impairment) older adults [mean age = 70.17 (SD = 8.5) years] from the BIOCARD study underwent longitudinal DTI (mean follow-up = 2.5 years, max = 4.7 years). White matter microstructure was quantified by fractional anisotropy (FA) and radial diffusivity (RD) values in global white matter tracts and medial temporal lobe (MTL) white matter tracts.

Results: Using longitudinal linear mixed effect models, we found that FA decreased over time and RD increased over time in both the global and MTL DTI composites, but the rate of change in these DTI measures was not related to level of CR. However, there were significant interactions between the CR composite score and age for global RD in the full sample, and for global FA, global RD, and MTL RD among those with normal cognition. These interactions indicated that among participants with a lower baseline age, higher CR composite scores were associated with higher FA and lower RD values, while among participants with higher age at baseline, higher CR composite scores were associated with lower FA and higher RD values. Furthermore, these relationships were not modified by *APOE*-ε4 genotype or level of vascular risk.

Conclusion: The association between level of CR and DTI measures differs by age, suggesting a possible neuroprotective effect of CR among late middle-aged adults that shifts to a compensatory effect among older adults.

Keywords: diffusion tensor imaging, cognitive reserve, brain maintenance, aging, white matter microstructure, vascular risk, *APOE*

INTRODUCTION

Cognitive reserve (CR) is commonly defined as an attribute of the brain that provides for better-than-expected cognitive performance in the presence of age- or disease-related brain changes (Stern et al., 2020; Reserve and Resilience, 2021)[1]. Although the neurobiological mechanisms underlying CR are not yet well understood, previous research suggests that certain lifetime experiences—including increased education, greater occupational complexity, higher literacy, and bilingualism—may reduce the impact of brain injury or disease on cognitive performance (Solé-Padullés et al., 2009; Brickman et al., 2011; Schreiber et al., 2016; Rentz et al., 2017). These lifetime experiences, in combination with genetic factors, are hypothesized to enable the brain to better cope with or compensate for brain aging or disease. The related concept of *brain maintenance* is often used to refer to the relative absence of age-related or disease-related changes in neural resources over time as a determinant of preserved cognitive performance. It is hypothesized that these same lifetime experiences, as well as other factors, may directly prevent or slow age- or disease-related brain changes, thereby reducing cognitive decline and clinical symptoms (Stern et al., 2020).

The present study examines one possible mechanism by which lifetime experiences may promote brain maintenance by investigating how proxies of cognitive reserve (including years of education, literacy, and vocabulary) affect brain white matter microstructural properties over time, as assessed by diffusion tensor imaging (DTI). DTI is a magnetic resonance imaging (MRI) technique for measuring the diffusion of water in tissue. Higher fractional anisotropy (FA), a measure of directional diffusion, and lower radial or mean diffusion (RD and MD, respectively) in white matter tracts are commonly considered to represent greater white matter structural "integrity" (Bennett and Madden, 2014), though their biological interpretability is limited (see Jones et al., 2013). Prior DTI studies have shown that FA decreases with age, whereas RD and MD increase with age, suggesting a decrease in white matter microstructural integrity with advanced age (e.g., Bennett and Madden, 2014; Bender et al., 2016). Of relevance to the current investigation, higher FA and lower RD or MD in white matter tracts have been linked to better cognitive performance among older adults (e.g., Sasson et al., 2013; Bennett and Madden, 2014; Coelho et al., 2021), suggesting that maintenance of white matter microstructural integrity with increasing age would be important for maintaining cognitive performance in aging.

Relatively few studies have investigated how cognitive reserve proxies, such as education, may affect white matter microstructure among middle-aged and older individuals with normal cognition and those with mild cognitive impairment (MCI). To our knowledge, these studies have all been cross-sectional in nature and results have been mixed. For instance, Teipel et al. (2009) found that cognitively normal older individuals with more years of education had higher FA values in medial temporal lobe regions and other cortical and subcortical structures, compared to those with less education. Similarly, Kaup et al. (2018) found that having occupations with greater cognitive complexity was associated with higher FA globally, with strongest effects in frontal and temporal lobes. Additionally, higher socio-economic status (Johnson et al., 2013), greater literacy (Resende et al., 2018), and bilingualism (Luk et al., 2011) were related to higher regional white matter FA among non-demented older adults. Although these studies suggest that greater educational or occupational achievement may have neuroprotective effects on white matter microstructure, other studies examining these relationships reported null results (Casaletto et al., 2020; Neth et al., 2020), or associations in the opposite direction. For example, Vaqué-Alcázar et al. (2017), found that cognitively normal older individuals with higher levels of education had lower FA measures in several white matter tracts. Likewise, higher CR composite scores that incorporated measures of education, occupation, and cognitive leisure activity were associated with lower FA in the corpus collosum among older participants with normal cognition or MCI (Arenaza-Urquijo et al., 2011).

The reason(s) for the discrepancy in results across prior studies remain unclear, but could be related to differences in white matter tracts examined and participant characteristics, including age, proportion of individuals at genetic risk for Alzheimer's disease (AD), level of vascular risk, and cognitive status (cognitively normal vs. non-demented, which includes cognitively normal and MCI participants). One goal of the current study, therefore, was to systematically investigate whether the relationship between a proxy measure of CR and white matter microstructural integrity is modified by participant age, *APOE*-ε4 genetic status (the main genetic risk factor for late-onset AD; Corder et al., 1993), and level of vascular risk. Additionally, to our knowledge, no prior studies have examined the impact of cognitive reserve proxies on brain white matter microstructure over time. To address these gaps in the literature, the present study uses DTI measures taken at multiple timepoints to examine whether lifetime experiences, measured by a CR composite proxy score, are associated with the level and/or rate of change in white matter microstructure over time (mean DTI follow-up = 2.5 years, max = 4.7 years). White matter microstructure was examined both globally (using the average across 8 major tracts) and within tracts connecting medial temporal lobe (MTL) structures. These tracts were chosen because they have previously been linked to CR proxies, as discussed above. Furthermore, while most prior studies on this topic focused on FA as a measure of white matter microstructure and had relatively small sample sizes (≤100 participants, e.g., Teipel et al., 2009; Arenaza-Urquijo et al., 2011; Luk et al., 2011; Johnson et al., 2013; Vaqué-Alcázar et al., 2017; Resende et al., 2018), the current study assessed both FA and RD and included 192 non-demented participants, including 166 with normal cognition and 26 with MCI.

MATERIALS AND METHODS

Study Design and Participant Selection

Participants included in the current study are part of the ongoing prospective, longitudinal BIOCARD study, which was initiated at the National Institutes of Health (NIH) in 1995. The BIOCARD

[1]Reserve and Resilience (2021). Framework for terms used in research of reserve and resilience. Available at: https://reserveandresilience.com/framework/ (Accessed October 18, 2021).

study has the overarching goal of identifying variables among individuals with normal cognition that could predict the onset of mild to moderate symptoms of AD. After providing written informed consent, 349 cognitively normal, primarily middle-aged participants were enrolled in the study. Approximately 75% of the participants had a family history of AD dementia. While the study was at the NIH, participants completed annual clinical and cognitive assessments, as well as biomarker assessments approximately every other year. The study was stopped in 2005 for administrative reasons and resumed at Johns Hopkins University (JHU) in 2009, upon approval by the JHU Institutional Review Board. Annual blood draws and clinical and cognitive evaluations were reinitiated in 2009. The biennial collection of MRI scans (including DTI) was resumed in 2015. Additional details on the resumption of other biomarker assessments are described in Pettigrew et al. (2020).

This study reports data from 192 non-demented participants with DTI data collected between 2015 and 2020. For the purposes of these analyses, "baseline" was defined as the first available DTI scan. Of note, the MRI scans collected at the NIH did not include DTI sequences, thus the first possible DTI scan in this cohort was acquired in 2015.

Cognitive and Clinical Assessment

The annual visits at JHU include a neuropsychological battery, clinical assessments, and a semi-structured interview based on the Clinical Dementia Rating Scale (CDR, Morris, 1993; see Albert et al., 2014 for details). The diagnosis of MCI (Albert et al., 2011) and dementia (McKhann et al., 2011) followed recommendations by the National Institutes on Aging and Alzheimer's Association working group reports. Three types of information were used as the basis for establishing a syndromic diagnosis (i.e., cognitively normal, MCI, impaired not MCI, or dementia): (1) clinical data reporting the individual's medical, neurological, and psychiatric status; (2) worsened cognitive performance on the neuropsychological battery, based on review of longitudinal testing from multiple domains and comparison to published norms; and (3) reports of changes in cognition by the individual and by collateral sources based on the CDR. Psychiatric, neurological, and medical information collected at the visit were used to identify the likely etiology(ies) of the syndrome for individuals judged to be impaired. When conflicting information from neuropsychological battery performance and the CDR interview were reported (e.g., the collateral source and/or participant reported changes in cognition in daily life, but cognitive testing did not show changes or vice versa), a diagnosis of Impaired not MCI was made (see Albert et al., 2014). Participants with a diagnosis of Impaired not MCI ($N = 29$) were included in the group of cognitively normal participants, but results were comparable when they were excluded from analysis (data not shown). All clinical diagnoses were made independently from knowledge of any biomarker measures.

MRI Acquisition

MRI scans were acquired on a 3 T Phillips Achieva scanner (Eindhoven, The Netherlands). The multi-modal protocol included magnetization-prepared rapid gradient echo (MPRAGE) scans used for anatomical reference and image registration (TR = 6.8 ms, TE = 3.1 ms, shot interval 3,000 ms, flip angle = 8°, FOV = 240 × 256 mm^2, 170 slices with 1 × 1 × 1.2 mm^3 voxels, and scan duration = 5 min 59 s). Diffusion-weighted images were acquired from a spin echo sequence (TR = 7.5 s, TE = 75 ms, FOV = 260 × 260, slice thickness = 2.2 mm, flip angle = 90, b-value = 700, number of gradients = 33, axial plane, in-plane resolution = 0.8281 × 0.8281 mm). DTI images from all participants were collected from the same scanner and processed with the same software and parameters.

DTI Processing

The DTI images were automatically pre-processed and segmented using MRICloud (Mori et al., 2016).[2] The tensor reconstruction and quality control followed the pipeline of DTIStudio (Jiang et al., 2006).[3] MRICloud is a web-based platform that uses a fully automated multiatlas image parcellation algorithm that combines the image transformation algorithm, Large Deformation Diffeometric Mapping, based on complementary contrasts (e.g., MD, RD, FA, and fiber orientation; Ceritoglu et al., 2009), and a likelihood fusion algorithm for DTI multiatlas mapping and parcellation (Tang et al., 2014). This generated 168 regions of interest (ROIs), from which DTI scalar metrics (3 eigenvalues) were extracted. The analyses focused on global and medial temporal FA and RD values. Global FA and RD values were calculated as the average of 8 major bilateral white matter tracts (fornix, cingulum, uncinate fasciculus, corona radiata, super longitudinal fasciculus, inferior frontal occipital fasciculus, corpus callosum, and posterior thalamic radiation, as used in prior work by this group; Soldan et al., 2022). Medial temporal FA and RD values were calculated as the average of 3 bilateral MTL white matter tracts (hippocampal cingulum, fornix, and uncinate fasciculus), which have previously been linked to episodic memory performance in the current cohort (Alm et al., 2020). The tracts included in each of these composites were chosen *a priori*, because they provide robust estimates of FA and RD using the automatic MRICloud pipeline across a broad range of ages and levels of neurodegeneration (Rezende et al., 2019). Composites were used to reduce the number of statistical comparisons, and because prior literature has not provided a clear indication of which specific tracts are related to measures of cognitive reserve or contribute to brain maintenance.

Cognitive Reserve Composite Score

Level of cognitive reserve (CR) was operationalized by a composite score that included three measures commonly used as proxies of CR, hypothesized to reflect lifetime cognitive experiences: (1) years of education; (2) scores from the National Adult Reading Test (NART; Nelson, 1982); and (3) scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary subtest (Wechsler, 1981). Both the NART and the

[2]https://braingps.mricloud.org
[3]www.MRIStudio.org

WAIS-R were collected at study baseline (i.e., between 1995–2005), when all participants were cognitively normal. These measures were standardized as z-scores then averaged to calculate the composite, given that they are highly correlated and load on a single factor in a factor analysis (for details, see Soldan et al., 2013). Prior studies have demonstrated this composite to be associated with better clinical and cognitive outcomes after adjusting for biomarkers of AD pathology (Soldan et al., 2013, 2015, 2017; Pettigrew et al., 2017).

Vascular Risk Composite Score

Vascular risk factors were established through self-report during a medical history interview and available medical records. A composite vascular risk score was calculated using a previously validated approach (Gottesman et al., 2017) that sums 5 dichotomous vascular risk factors (each coded as 0 = absent, 1 = recent/remote): diabetes, hypertension, hypercholesterolemia, obesity (based on body mass index >30 kg/m^2), and current smoking (i.e., within the past 30 days).

APOE Genotype

APOE genotypes were determined by restriction endonuclease digestion of PCR-amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). Genotypes were coded dichotomously (*APOE*-ε4 carriers = 1, non-carriers = 0).

Statistical Analyses

Group differences in demographic and descriptive statistics were assessed by Wilcoxon rank sum tests for continuous variables and chi-square tests for binary variables.

Longitudinal linear mixed effects models were used to examine the associations of the CR composite score with level of, and longitudinal change in, global and MTL FA and RD (see **Supplementary Material 1**). These models included linear effects of time and were specified with random intercepts and slopes (Laird and Ware, 1982; Diggle et al., 1994). Separate models were run for each DTI measure, which served as the dependent variable, including baseline measures and all available follow-up. Time was modeled as a continuous variable in the unit of year. All other continuous variables were standardized before model fitting. The primary set of models included the following predictors: time (years from baseline), sex, age at first DTI scan, diagnosis at time of scan (normal vs. MCI), CR composite score, and the interaction (cross-product) of each predictor with time. The main effect of the CR composite score, and the two-way CR composite score × time interaction, were of primary interest, as these terms reflect differences in levels and rates of change of the DTI measures (respectively) as a function of the CR composite score.

The second set of linear mixed regression models tested whether the relationship between the CR composite score and level of, and longitudinal change in, the DTI measures was modified by age, *APOE*-ε4 genetic status, and the vascular risk composite score, with separate models run for each of these variables of interest. This was accomplished by re-running the models above, this time including the additional relevant two-way and three-way interactions. For example, for the models assessing the impact of age, the CR composite score × age interaction indicates whether the association of the CR composite score and levels of the DTI measures differed by baseline age, whereas the three-way CR composite score × age × time interaction indicates whether the relationship between the CR composite score and rates of change in the DTI measures differed by baseline age.

Sensitivity analyses examined whether the patterns of results changed when individuals with MCI were excluded. Separate models were not run for the participants with MCI given the small sample size ($n = 26$). Estimates and p-values are reported, and p-values < 0.05 were considered significant. All analyses were run in R, version 3.5.0.

Research Data

Anonymized BIOCARD study data are available upon request from qualified investigators; for more details, visit www.biocard-se.org.

RESULTS

Study Sample Characteristics

Baseline descriptive characteristics of all participants included in the analyses, stratified by diagnosis, are reported in **Table 1**. Compared to those with normal cognition, individuals with MCI were older, less likely to be White, performed worse on the Mini-Mental State Examination, had lower CR composite scores, higher vascular risk scores, and lower global and MTL FA values, and higher global and MTL RD values (all $p < 0.01$). Additionally, the mean follow-up time between participants' first and last DTI scan was less for participants with MCI. Of note, higher CR composite scores were correlated with higher MMSE scores across the non-demented participants, partialling out age and sex, [$r(188) = 0.39$, $p < 0.01$], and in the cognitively normal subgroup [$r(162) = 0.26$, $p < 0.01$].

Association of Baseline CR With Level of and Change in DTI Measures

In both the full sample ($n = 192$) and the subset with normal cognition ($n = 166$), there were significant effects of time for all DTI measures, indicated by decreases in FA values and increases in RD values over time, in both the global and MTL DTI composites (all $p < 0.001$). However, there were no significant CR × time interactions in either group (all $p > 0.14$), indicating that the rate of change in DTI measures over time does not differ by level of CR. Additionally, in reduced models that excluded the non-significant CR × time interaction terms, there were no main effects of CR on global or MTL FA or RD in the full sample (all $p > 0.11$). Among the subset with normal cognition, there was a significant main effect of CR on MTL RD only [estimate = −0.141, 95% CI (−0.244, −0.039), $p = 0.007$; all other $p > 0.08$], indicating that higher CR composite scores were associated with lower RD in the MTL tracts.

TABLE 1 | Baseline characteristics of participants included in the analyses. Values reflect mean (SD) unless otherwise indicated.

Variable	All subjects in analysis *N* = 192	Cognitively normal at baseline *N* = 166	MCI at baseline *N* = 26
Age at baseline DTI scan	70.2 (8.50)	69.5 (8.17)	74.4 (9.53)*
Sex female, *N* (%)	120 (62.5%)	105 (63.3%)	15 (57.7%)
White race, *N* (%)	186 (96.9%)	164 (98.8%)	22 (84.6%)*
APOE4 carriers, *N* (%)	62 (32.3%)	54 (32.5%)	8 (30.8%)
Years of education	17.3 (2.29)	17.3 (2.22)	17.1 (2.72)
MMSE at baseline	29.0 (1.24)	29.3 (0.93)	27.3 (1.57)*
CR composite score	0.13 (0.78)	0.21 (0.70)	−0.37 (1.04)*
Global FA	0.47 (0.02)	0.47 (0.02)	0.45 (0.02)*
MTL FA	0.41 (0.02)	0.41 (0.02)	0.39 (0.02)*
Global RD	7.0^{-4} (5.10^{-5})	6.9^{-4} (4.85^{-5})	7.3^{-4} (5.47^{-5})*
MTL RD	9.3^{-4} (7.99^{-5})	9.2^{-4} (7.58^{-5})	1.0^{-3} (7.44^{-5})*
Number of DTI scans over time [range]	2.2 (0.73) [1–3]	2.3 (0.72) [1–3]	1.9 (0.73) [1–3]
Time between first and last DTI scan, in years [range]	2.5 (1.49) [0–4.7]	2.7 (1.46) [0–4.7]	1.8 (1.51) [0–4.2]*
Composite vascular risk score	1.4 (1.09)	1.3 (1.06)	2.0 (1.08)*

**Significant difference between groups, $p < 0.01$, using Wilcoxon rank sum tests for continuous variables and chi-square tests for dichotomous variables.*
CR, cognitive reserve. DTI, diffusion tensor imaging. FA, fractional anisotropy. MCI, mild cognitive impairment. MMSE, Mini-Mental State Examination (Folstein et al., 1975); MTL, medial temporal lobe; RD, radial diffusivity.

TABLE 2 | Results of the reduced longitudinal mixed effects models examining whether the relationship between the CR composite score and white matter microstructure differs by baseline age (see text for details).

Model Predictors	Global FA		MTL FA		Global RD		MTL RD	
	Estimate (95% CI)	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
Full Sample								
CR Composite	0.017 (−0.104, 0.137)	0.788	−0.006 (−0.129, 0.115)	0.918	−0.037 (−0.146, 0.072)	0.505	−0.051 (−0.161, 0.059)	0.369
CR Composite × age	−0.1 (−0.204, 0.004)	0.064	−0.063 (−0.164, 0.039)	0.232	**0.127 (0.031, 0.224)**	**0.011***	0.067 (−0.029, 0.162)	0.178
CR Composite × time	0.008 (−0.033, 0.049)	0.717	0.028 (−0.014, 0.071)	0.19	−0.002 (−0.032, 0.027)	0.888	−0.021 (−0.049, 0.008)	0.159
Cognitively normal								
CR Composite	0.084 (−0.047, 0.215)	0.214	0.04 (−0.098, 0.177)	0.577	−0.092 (−0.21, 0.027)	0.134	−0.096 (−0.221, 0.029)	0.137
CR Composite × age	**−0.161 (−0.289, −0.033)**	**0.015***	−0.092 (−0.22, 0.037)	0.167	**0.211 (0.093, 0.33)**	**0.001***	**0.127 (0.004, 0.249)**	**0.047***
CR Composite × time	0.006 (−0.039, 0.051)	0.787	0.026 (−0.021, 0.072)	0.287	−0.006 (−0.039, 0.026)	0.708	−0.02 (−0.051, 0.01)	0.201

**$p < 0.05$.*

For the model covariates (from the reduced models that excluded the non-significant interaction terms), in the full sample, higher age at baseline was associated with lower FA and higher RD values in the global and MTL DTI composites (all $p < 0.001$), and female sex was associated with lower global and MTL RD values (both $p < 0.04$). Furthermore, an MCI diagnosis was associated with lower global and MTL FA values (both $p < 0.04$), as well as higher global and MTL RD values (both $p < 0.03$). In addition, the rates of change in global and MTL FA values, and in global RD values, over time were greater among older participants, as indicated by significant age × time interactions (both $p < 0.05$), with a similar trend for MTL RD values ($p = 0.051$). The patterns of covariate effects were similar for the subset with normal cognition, except that the age × time interactions were only significant for the global RD values ($p = 0.009$), whereas these interactions were trending for the global and MTL FA values and MTL RD values (all $p \leq 0.10$).

Interaction Between CR and Age on DTI Measures

In both the full sample ($n = 192$) and the subset with normal cognition ($n = 166$), there were no significant CR × age × time interactions for any of the DTI measures (all $p > 0.63$), indicating that the associations between the CR composite score and rates of change in the DTI measures over time do not differ by baseline age. The results for the reduced models, which excluded the non-significant CR × age × time interaction terms, are shown in **Table 2**. In the full sample, there was a CR × age interaction for global RD (**Figures 1A,B**). Additionally, among the subset with normal cognition, there were significant CR × age interactions for global FA (**Figures 2A,B**), global RD (**Figures 2C,D**), and MTL RD (**Figures 2E,F**). For both groups, these CR × age interactions indicate that the relationship of the CR composite score to baseline levels of the DTI measures differed for individuals of younger compared to older baseline

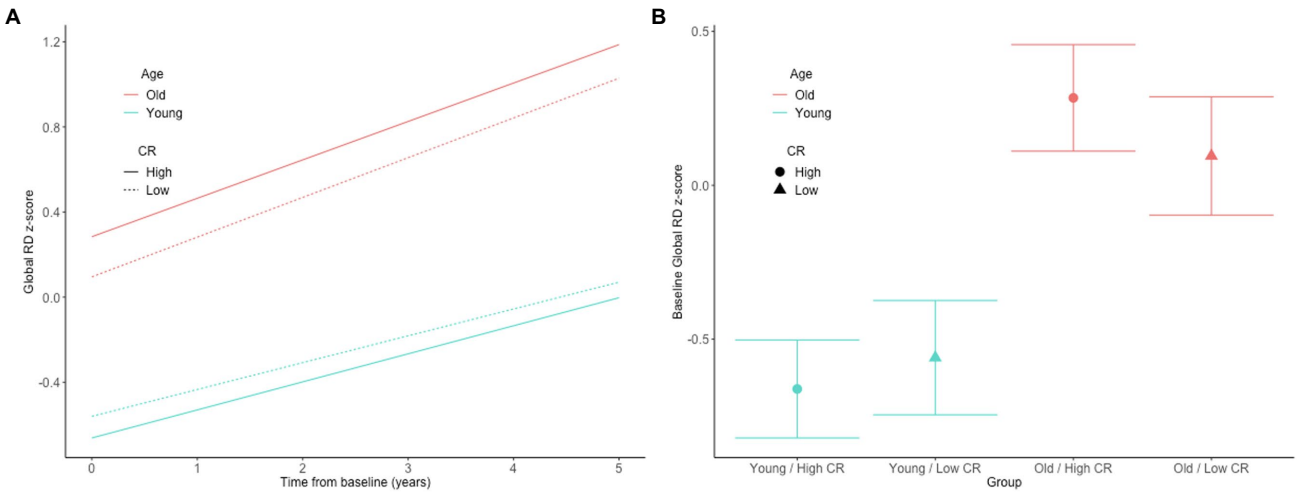

FIGURE 1 | Estimates of the association between CR composite scores and age in relationship to longitudinal change in **(A)** and baseline level of **(B)** white matter microstructure, as measured by global RD in the full, non-demented sample. The CR composite score and age were dichotomized by median split for illustration purposes, but treated as continuous variables in the linear mixed effects models.

ages. Specifically, among younger adults, higher CR composite scores were associated with higher FA values and lower RD values at baseline; in contrast, among older adults, higher CR composite scores were associated with lower FA values and higher RD values at baseline. Note that while age and CR were dichotomized for illustration purposes, they were modeled as continuous variables in the statistical analyses.

When the models were restricted to the $n = 155$ individuals who were cognitively normal at *both* their first and last DTI scan, the CR × age interactions for global FA (estimate = −0.163, 95% CI (−0.289, −0.036), $p = 0.013$), global RD (estimate = 0.215, 95% CI (0.099, 0.33), $p < 0.001$), and MTL RD (estimate = 0.124, 95% CI (0.003, 0.246), $p = 0.05$) remained significant.

In exploratory analyses, there were similar CR × age interactions for the majority of the individual white matter tracts included in the global composite (see **Supplementary Table S1**), suggesting these effects are quite widespread, rather than driven by tract-specific effects. Consistent with the results of the global composite score, none of the CR × age × time interactions were significant (all $p > 0.10$, data not shown).

Interaction Between CR and *APOE*-ε4 Genotype Status on DTI Measures

In both the full sample ($n = 192$) and the subset with normal cognition ($n = 166$), there were no significant CR × *APOE*-ε4 × time interactions for any of the DTI measures (all $p > 0.33$); similarly, in the reduced models that excluded these non-significant 3-way interaction terms, there were no significant CR × *APOE*-ε4 interactions (all $p > 0.35$). This indicates that the associations between the CR composite score and level of, and rate of change in the DTI measures over time, did not differ by *APOE*-ε4 genotype status. Additionally, *APOE*-ε4 genotype status was unrelated to the levels of (all $p > 0.09$), and rate of change over time in (all $p > 0.07$), the DTI measures.

Interaction Between CR and Vascular Risk on DTI Measures

In both the full sample ($n = 192$) and the subset with normal cognition ($n = 166$), there were no significant CR × vascular risk score × time interactions for any of the DTI measures (all $p > 0.57$); similarly, in the reduced models that excluded these non-significant 3-way interaction terms, there were no significant CR × vascular risk score interactions (all $p > 0.68$). This indicates that the associations between the CR composite score and level of, and rate of change in the DTI measures over time, did not differ by level of vascular risk. Additionally, the vascular risk score was unrelated to the levels of (all $p > 0.10$), and rate of change in (all $p > 0.38$), the DTI measures.

DISCUSSION

This study examined whether lifetime experiences, as measured by a CR composite score, are related to the level of, and short-term rate of change in white matter microstructural integrity, as measured by global and MTL FA and RD values derived from DTI. The primary finding is that the relationship between the CR composite score and white matter microstructure differed by baseline age, such that among participants with younger baseline ages, higher CR composite scores tended to be associated with higher FA and lower RD scores, whereas among older participants, higher CR scores were related to lower FA and higher RD scores. Furthermore, the relationship between the CR composite score and white matter microstructure was not modified by *APOE*-ε4 genetic status or level of vascular risk. Taken together, these results suggest that among individuals in late middle age, greater educational and intellectual attainment may be associated with better global white matter microstructure, reflecting neuroprotective effects of these lifetime experiences.

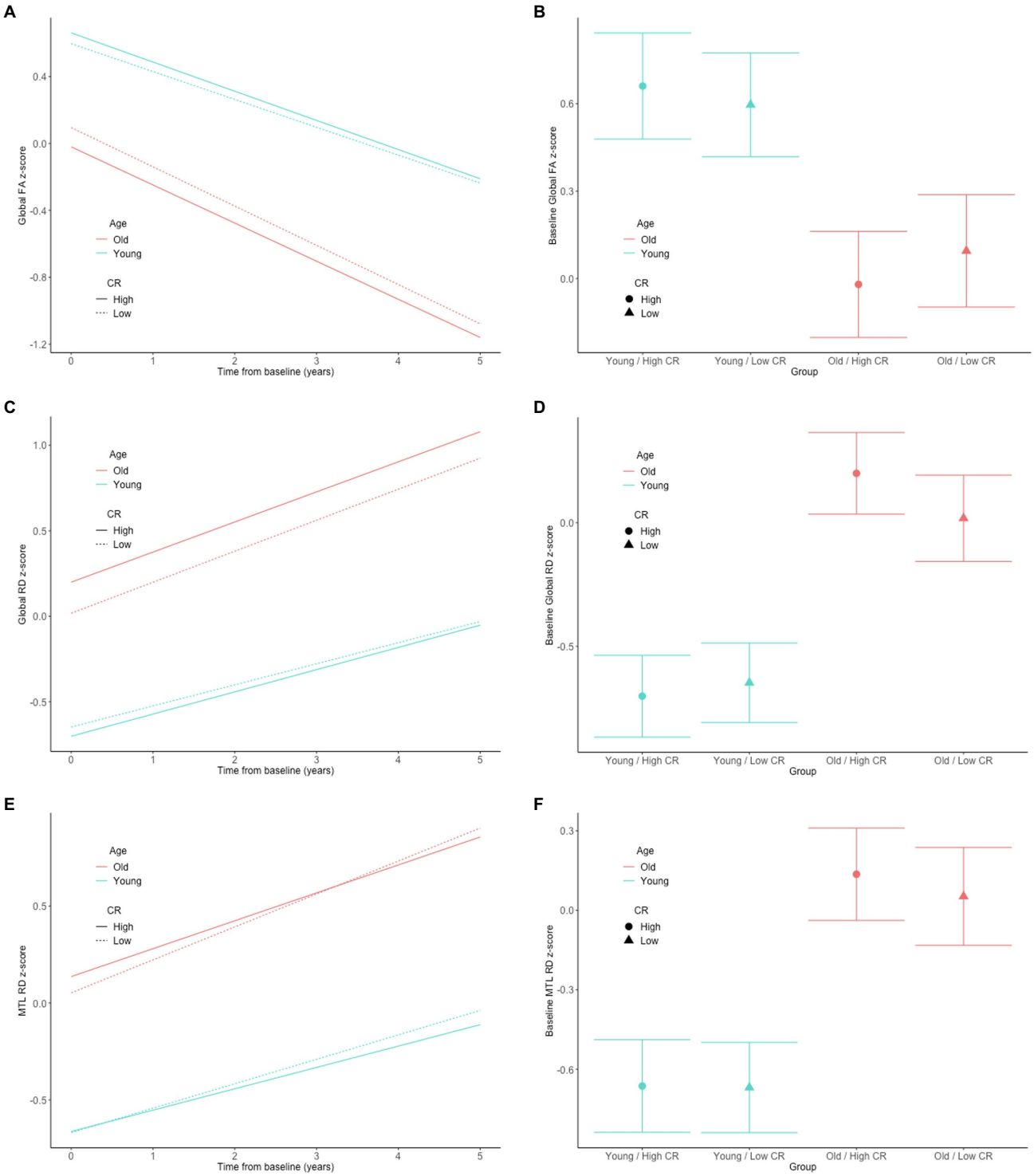

FIGURE 2 | Estimates of the association between CR composite scores and age in relationship to longitudinal change in (left) and baseline level of (right) white matter microstructure, as measured by global FA **(A,B)**, global RD **(C,D)**, and MTL RD **(E,F)** in the cognitively normal sample. The CR composite score and age were dichotomized by median split for illustration purposes, but treated as continuous variables in the linear mixed effects models.

In contrast, among older adults, these same experiences are associated with worse white matter microstructural integrity, potentially reflecting a greater ability to tolerate or compensate for age and/or disease-related declines in white matter integrity among those with higher than lower CR scores, as discussed in greater detail below.

To our knowledge, this is the first study to evaluate the relationship between CR proxies and DTI-derived brain white matter microstructure over time. Consistent with prior literature, we found that global and MTL white matter microstructure decreased over time, particularly among older participants (e.g., Bennett and Madden, 2014; Bender et al., 2016). However, we found no evidence of an association between lifetime experiences, as measured by a CR composite score, and short-term rate of change in global or MTL white matter microstructure, and no evidence that the CR proxy score reduced age-related changes in the white matter microstructure over time. Although these results provide preliminary evidence suggesting that lifetime experiences do not slow or prevent short-term changes in white matter microstructure among older adults, future studies including a larger array of CR proxies, and longer DTI follow-up, are needed to replicate these findings.

Our finding of an age-dependent relationship between the CR proxy score and white matter microstructural measures may help explain the inconsistencies in the literature, as prior studies to date have been quite mixed (as described above). For example, a large cross-sectional study ($N > 600$) found that greater occupational complexity in young to middle-adulthood was associated with higher FA globally and in all four lobes 10–15 years later, when participants were in middle age (Kaup et al., 2018). This is consistent with our finding of a more positive relationship between higher educational and intellectual achievement and higher global FA values among participants with lower baseline ages. Furthermore, in the present study, the interactions between the CR composite score and baseline age were particularly evident among the participants with normal cognition (relative to the full non-demented sample) and remained significant in the subset of individuals who were cognitively normal at all of their DTI time points. This may suggest that the neuroprotective effects of certain lifetime experiences on white matter microstructure decline after middle age, potentially because the beneficial effects of these lifetime experiences on white matter microstructure are smaller than age and disease-related changes, and are eventually overwhelmed by the latter. Consistent with this hypothesis, the estimated age-related difference in the level and rate of change in both FA and RD was greater than the CR-related difference in these measures (see **Figures 1, 2** for an illustration).

Our results are also broadly consistent with a prior study from our cohort, which reported that participants with higher CR composite scores had lower white matter hyperintensity levels when they were largely in late middle age (Pettigrew et al., 2020), providing evidence for a beneficial effect of educational and intellectual attainment on aspects of white matter structure. Furthermore, although in both studies the CR composite score was not related to the short-term rate of change in the white matter structural measures, the finding that participants with higher CR proxy scores (and lower baseline ages) had more intact white matter may be consistent with the concept of brain maintenance. Specifically, given that baseline measures in white matter indices were already different among participants with higher vs. lower CR scores may indicate that these white matter measures were influenced by educational and intellectual attainment at an earlier time point, and that these lifetime measures may act over longer time periods. Future studies that examine structural brain changes among middle-aged participants over longer time periods are needed to further test this hypothesis.

The finding that among participants with higher baseline ages, higher CR scores tended to be associated with reduced white matter integrity, as measured by both FA and RD, is consistent with prior studies reporting negative associations between level of education and FA values among cognitively normal and MCI participants (Arenaza-Urquijo et al., 2011; Vaqué-Alcázar et al., 2017). These results may suggest that while neuroprotective effects of higher educational and intellectual attainment on white matter microstructure are not measurable at older ages, these experiences instead allow individuals to tolerate greater amounts of age and/or disease-related changes in white matter microstructure, while maintaining cognitive performance over time. It is noteworthy that, although the impact of white matter microstructural measures on cognitive performance were not examined in this study, higher CR composite scores were correlated with better global cognitive performance, as measured by MMSE scores. This suggests that despite potentially having worse white matter microstructure, participants with higher educational and intellectual attainment tended to perform better cognitively. Taken together with the lack of association between the CR composite score and short-term rate of change in white matter microstructure over time (described above), the results from participants with older baseline ages are more consistent with the concept of cognitive reserve, rather than brain maintenance.

Although not examined in the present study, a possible mechanism by which higher educational or intellectual attainment may allow individuals to compensate for age or disease-related structural brain changes is by fostering functional network connectivity. For example, prior resting-state functional MRI (fMRI) studies among cognitively normal older adults have linked higher educational attainment (Arenaza-Urquijo et al., 2013; Perry et al., 2017), as well as greater engagement in cognitively stimulating leisure activities (Soldan et al., 2021) to greater functional network connectivity and improved cognitive performance. Additionally, task-based fMRI studies have provided evidence that older participants with high CR may have more efficient functional brain networks or may be able to rely on alternate or compensatory functional networks in the presence of neurodegenerative changes (Steffener et al., 2011; Franzmeier et al., 2017; Stern et al., 2018). This interpretation is also consistent with the "less wiring, more firing hypothesis," whereby increased functional activity of intact pathways may offset declines in white matter structural integrity, such as those measured by DTI (Daselaar et al., 2015). Enhancements in functional connectivity (e.g., greater network efficiency, capacity, or flexibility; Barulli and Stern, 2013) may support maintained cognitive performance in the presence of age or disease-related brain changes, and be one mechanism by which educational and intellectual attainment influence cognitive and clinical outcomes.

Exploratory analyses further suggested that the interaction between age and CR on white matter microstructure was evident in the majority of the individual tracts included in the composite measures. Conceptually, it seems reasonable that fairly broad measures of lifetime experience (i.e., education and literacy levels) would have global effects on the brain, as opposed to highly localized effects. However, future studies are needed to replicate this finding.

In this study, we found no evidence that the relationship between the CR composite score and level of, or rate of change in white matter microstructural integrity was modified by *APOE*-ε4 genotype. Additionally, *APOE*-ε4 genotype was unrelated to the level of, or rate of change in, global or MTL white matter microstructure, which is consistent with prior studies among cognitively normal older adults (Honea et al., 2009; Heise et al., 2011; Patel et al., 2013). As suggested by prior literature, *APOE*-ε4 has a greater impact on AD pathology, particularly amyloid burden (Morris et al., 2010; Resnick et al., 2015; Toledo et al., 2015; Pletnikova et al., 2018; Baek et al., 2020), rather than directly on white matter integrity, although we cannot rule out the possibility that *APOE*-ε4 affects axonal and synaptic integrity in ways that are not measurable through current DTI technologies (Adalbert et al., 2007).

We also found that vascular risk, as measured by a composite score, did not modify the relationship between CR and white matter microstructure. This suggests similar relationships between educational and intellectual attainment and white matter microstructure among individuals with higher and lower levels of vascular risk. However, the usage of a composite score precludes us from concluding that results would be the same for individual vascular risk factors. Additionally, the vascular risk composite score was unrelated to DTI white matter microstructure. This latter result appears inconsistent with prior studies that have found relationships between higher vascular risk (including hypertension, obesity, and diabetes) and poorer white matter integrity, as indexed by lower FA among middle-aged and older adults (e.g., Falvey et al., 2013; Zhang et al., 2018; Ingo et al., 2021). These null results may be attributed to somewhat lower levels of vascular risk among participants in the present study compared to other cohorts, as well as the high level of education among our participants that may enable them to more effectively manage their vascular conditions through medications.

Although several studies have examined the relationship of lifetime experiences to white matter microstructure, the neurobiological mechanisms underlying these associations are not well understood. Prior research has predominantly focused on the role of brain-derived neurotrophic factor (BDNF) as one possible mechanism. For example, prior studies in rodent models have demonstrated that BDNF is upregulated in brain regions including the hippocampus among animals exposed to enriched environments that provide more cognitive and physical stimulation (Ickes et al., 2000). BDNF is known to support neurogenesis, as well as synaptic plasticity, such as by enhancing synaptic vesicle movement and docking or increasing long-term potentiation, which is important for learning and memory (Pozzo-Miller et al., 1999; Rossi et al., 2006). Animal models have also shown that oligodendrocytes, which are myelinating cells that wrap around axons, promote BDNF production in the spinal cord and brain (Dougherty et al., 2000; Bradl and Lassmann, 2010; Ramos-Cejudo et al., 2015). This suggests that higher BDNF levels may help to preserve white matter microstructure/myelination. In an effort to extend these findings to humans, Ward et al. (2015) proposed that the *BDNF* Val66Met polymorphism interacts with CR to enhance executive function (Ward et al., 2015). Moreover, Collins and colleagues found that early-life education was associated with increased serum levels of BDNF in old age (Collins et al., 2021). Although much less is known about variables that regulate BDNF levels in humans, these findings suggest that early-life enrichment experiences, such as education, as well as lifelong experiences that promote literacy, may enhance the production of BDNF or other neurotrophic factors, thereby helping to maintain white matter microstructure across the lifespan. Lifetime experiences may also alter synaptic architecture or neurotransmitter transmission to promote resilience against disease-related pathology (Arnold et al., 2013; Garibotto et al., 2013; Robertson, 2013; Boros et al., 2017). Future studies are needed to further address these possibilities.

This study has limitations. First, DTI provides only an indirect measure of white matter integrity (Jones et al., 2013). Thus, the results of this study are limited by the use of this technique, and future studies could expand this work by using DTI in conjunction with other measures of white matter integrity (Bennett and Madden, 2014). Furthermore, this study evaluated FA and RD composites to minimize the number of multiple comparisons, though future studies might also evaluate other DTI measures, such as axial diffusivity. The BIOCARD cohort is highly educated, primarily White, and by design has a strong family history of AD, therefore limiting the generalizability of these results. Additionally, we focused on a single measure of lifetime experiences—a CR proxy score—and therefore cannot address the extent to which other CR proxies, such as occupation or bilingualism, differentially influence white matter microstructure. Finally, on average, there were only 2.5 years between an individual's first and last DTI scan, which is a brief snapshot of brain changes that may occur over decades. It is possible, therefore, that results may differ over longer follow-up periods.

DATA AVAILABILITY STATEMENT

Anonymized data used in the analyses presented in this report are available on request from qualified investigators (www.biocard-se.org).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA, AS, and CP contributed to the study design. RB, AS, and CP drafted the manuscript and interpreted the data. YZ performed the statistical analyses and contributed to the interpretation of the data. AF contributed to processing the MRI scans. All authors revised the manuscript for content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.859826/full#supplementary-material

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Area Deprivation Index as a Surrogate of Resilience in Aging and Dementia

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Area deprivation index (ADI), a tool used to capture the multidimensional neighborhood socioeconomic disadvantage across populations, is highly relevant to the field of aging and Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD). ADI is specifically relevant in the context of resilience, a broad term used to explain why some older adults have better cognitive outcomes than others. The goal of this mini-review is three-fold: (1) to summarize the current literature on ADI and its link to cognitive impairment outcomes; (2) suggest possible mechanisms through which ADI may have an impact on AD/ADRD outcomes, and (3) discuss important considerations when studying relations between ADI and cognitive as well as brain health. Though difficult to separate both the upstream factors that emerge from high (worse) ADI and all the mechanisms at play, ADI is an attractive proxy of resilience that captures multifactorial contributors to the risk of dementia. In addition, a life-course approach to studying ADI may allow us to capture resilience, which is a process developed over the lifespan. It might be easier to build, preserve or improve resilience in an environment that facilitates instead of hindering physical, social, and cognitively beneficial activities. Neighborhood disadvantage can adversely impact cognitive impairment risk but be at the same time a modifiable risk factor, amenable to policy changes that can affect communities.

Keywords: area deprivation index, resilience, socioeconomic, cognitive impairment, dementia

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INTRODUCTION

Chronological age is the strongest risk factor for dementia, and dementia prevalence is expected to rise due to the aging of the population, reaching potentially close to 150 million cases worldwide by 2050 (Livingston et al., 2017), with most of the new cases of dementia occurring in the low and middle-income countries (LMICs) (Ashby-Mitchell et al., 2020). Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) have devastating consequences not only for the individual but have a major impact on the family, society, and the health care economies (Petersen, 2018; Stephan et al., 2018; Tochel et al., 2019). Thus, interventions that target modifiable AD/ADRD risk factors are of utmost importance.

Persons from historically underrepresented groups and socially disadvantaged populations are disproportionately affected by AD/ADRD (Powell et al., 2020). Research is still limited about the association between neighborhood socioeconomic deprivation with cognitive impairment (Marengoni et al., 2011; Yaffe et al., 2013; Kind and Buckingham, 2018; McCann et al., 2018). However, conditions adversely associated with a person's risk for cognitive impairment (e.g., higher rates of cardiovascular diseases, diabetes, multimorbidity, stress levels, health behaviors) (Roberts and Knopman, 2013; Roberts et al., 2015; Resende et al., 2019) are also associated with living in socioeconomically deprived neighborhoods (Kind and Buckingham, 2018; McCann et al., 2018; Chamberlain et al., 2020).

Area level deprivation measures, like the area deprivation index (ADI) (Kind and Buckingham, 2018), encompass geographic area-based estimates of the socioeconomic disadvantage of neighborhoods. These composite measures integrate indicators for several social determinants of health (Powell et al., 2020), such as education, employment, housing, and poverty (Kind and Buckingham, 2018; McCann et al., 2018), and allow us to study how living in socioeconomically disadvantaged neighborhoods may adversely affect health and disease outcomes (Kind and Buckingham, 2018; McCann et al., 2018; Chamberlain et al., 2020).

The concept of resilience has been used to explain better cognitive outcomes in a subset of individuals in the context of aging and dementia and is based on complex, interactive mechanisms (Stern et al., 2020) involving a person's demographics, genetics, and exposures over the lifespan. Therefore, cognitive impairment (in part due to low resilience) could also be affected by neighborhood socioeconomic disadvantage, as socioeconomically deprived neighborhoods experience more difficult living, working, and learning conditions (Zuelsdorff et al., 2020) and adverse impact on their health and health behaviors.

In this work, we will review literature on ADI as a measure of socioeconomic deprivation of neighborhoods and expand on the potential mechanisms through which ADI could be associated with resilience in aging and dementia. We hypothesize that ADI, reflective of comorbidities and lifestyles at present and through the lifespan, would be a useful quantifiable measure of resilience reflective of cognitive impairment risk due to socioeconomic status differences. We use resilience here in the context of better-than-expected cognitive performance (Arenaza-Urquijo and Vemuri, 2020).

AREA DEPRIVATION INDEX

The effect of multiple individual measures of socioeconomic status (e.g., education, income, occupation) on health has been studied more in the past but recently, more attention is focused on the effect of neighborhood context on health (Chamberlain et al., 2022). The ADI is a composite measure of neighborhood socioeconomic disadvantage at the Census Block Group level, - the closest approximation to a "neighborhood" - using 17 census measures including education, employment, income, poverty, and housing characteristics (Singh, 2003; Kind et al., 2014). ADI is publicly available, and values can be downloaded from the Neighborhood Atlas® website[1], the University of Wisconsin, School of Medicine and Public Health (Kind et al., 2014; Kind and Buckingham, 2018). Briefly, the ADI values are provided in national percentile rankings at the block group level (i.e., a block group with a ranking of 1 shows the lowest level of neighborhood disadvantage within the nation, but a ranking of 100 suggests the highest level of neighborhood disadvantage). The ADI values are also provided in deciles created by ranking the ADI within each state (a block group ranking of 1 shows the lowest level of neighborhood disadvantage within the state, and 10 specifies the highest ADI (most disadvantaged) within the state).

AREA DEPRIVATION INDEX AS A SURROGATE OF LIFESTYLE AND MORBIDITY

Health risk behaviors (e.g., smoking, drinking, being sedentary) and health-promoting behaviors (e.g., physical exercise, interpersonal interaction, spiritual growth, stress management) constitute one's lifestyle (Wang and Geng, 2019). In the US, nearly 40% of deaths could be linked to lifestyle-related behavioral factors (e.g., tobacco use, poor diet, physical inactivity, alcohol consumption), which are associated with an increased chronic disease burden (including AD/ADRD) but are modifiable (Mokdad et al., 2004; Bauer et al., 2014). Lifestyle might not be entirely a personal choice; it is influenced by various social factors, including socioeconomic status, and could even mediate the relationship between socioeconomic status and one's health (Wang and Geng, 2019).

A recent report estimated that twelve modifiable risk factors (i.e., less education, physical inactivity, low social contact, alcohol consumption, hypertension, hearing impairment, smoking, obesity, depression, diabetes, traumatic brain injury, and air pollution) could account for 40% of dementia cases worldwide (Livingston et al., 2020). Several of these modifiable risk factors are associated also with living in socioeconomically deprived neighborhoods, as aforementioned (Roberts and Knopman, 2013; Roberts et al., 2015; Kind and Buckingham, 2018; McCann et al., 2018; Resende et al., 2019; Chamberlain et al., 2020). Neighborhoods have characteristics that can impact health behaviors, environmental factors related to socioeconomic status (e.g., lead exposure, air pollution), and socioeconomically deprived neighborhoods could provide less opportunities for cognitively beneficial activities (e.g., social, recreational, physical, cognitive activities) (Diez Roux and Mair, 2010; Krell-Roesch et al., 2017, 2019; George et al., 2020; Hunt et al., 2021). The impact of preventive interventions (e.g., addressing these modifiable AD/ADRD risk factors) could be high and potentially even higher for LMICs where more dementia cases occur (Livingston et al., 2020).

[1]https://www.neighborhoodatlas.medicine.wisc.edu/

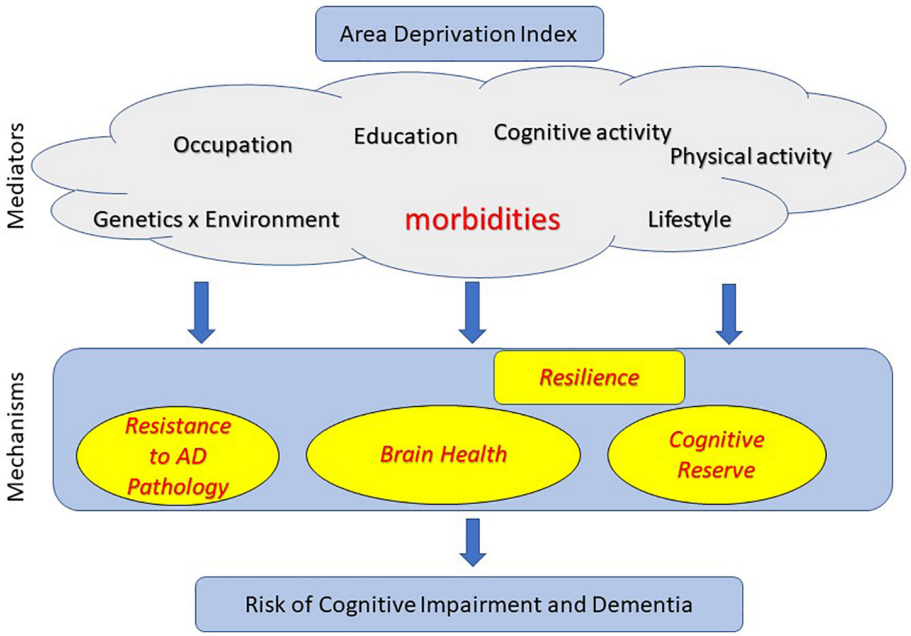

FIGURE 1 | Mechanisms through which area deprivation index (ADI) may influence risk of cognitive impairment, Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD).

Chronic conditions and multimorbidity (e.g., the co-occurrence of ≥2 conditions in a person) are more prevalent in persons with lower socioeconomic status (Rawshani et al., 2016; Pathirana and Jackson, 2018; Chamberlain et al., 2022). Living in socioeconomically deprived neighborhoods adversely affects not only health (e.g., higher rates of cardiovascular diseases, diabetes, stress levels, premature mortality, worse all-cause, and cardiovascular mortality), but also health behaviors, access to food, safety, and education, (Kind and Buckingham, 2018; McCann et al., 2018; Chamberlain et al., 2020) beyond also the effects of individual measures of socioeconomic status (Ludwig et al., 2011; Rawshani et al., 2016). As many of these conditions are associated with mild cognitive impairment (MCI) and dementia risk, area-level socioeconomic deprivation could contribute to late-life cognitive impairment (Roberts and Knopman, 2013; Roberts et al., 2015; Resende et al., 2019).

Area deprivation index was associated with multimorbidity in a cohort of nearly 200,000 people even after adjusting for education (an individual-level socioeconomic variable). This association was stronger in younger ages and women (Chamberlain et al., 2020). In addition, the risk of most chronic conditions (e.g., hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, diabetes, dementia, depression, schizophrenia, substance abuse disorders, and anxiety) increased with increasing ADI (Chamberlain et al., 2022).Patterns of associations were in general, similar for men and women, but the associations were modestly stronger in women for some of the chronic conditions (hyperlipidemia, diabetes, cardiac arrhythmias, coronary artery disease, arthritis, osteoporosis, and depression) (Chamberlain et al., 2022). However, not all studies point to such conclusions, as previous reports suggest that the socioeconomic gradient is steeper for men than women for health outcomes, except possibly heart disease (Deguen et al., 2010; Phillips and Hamberg, 2015).

Area deprivation index is estimated independent of sex and gender, it is a composite measure capturing education, employment, income, poverty, and housing characteristics at the census block group level, as aforementioned. However, sex and gender disparities and neighborhood disadvantage disparities need to be considered while studying resilience in AD/ADRD. The sex- and gender-specific changes in the balance between resilience and pathogenesis risk factors vary over the AD/ADRD disease course; however, the cause of such sex and gender differences is not clearly understood (Mielke et al., 2022).

In summary, ADI as a variable is reflective of a multitude of factors as illustrated in **Figure 1**. While associations may vary in different populations, ADI may be reflective of lifestyle broadly and much more closely associated to comorbidities.

MECHANISMS THROUGH WHICH AREA DEPRIVATION INDEX MAY INFLUENCE COGNITIVE, ALZHEIMER'S DISEASE AND ALZHEIMER'S DISEASE RELATED DEMENTIAS OUTCOMES

There has been tremendous research in the field of protective and risk factors that influence cognitive outcomes in aging and dementia. There is increasing understanding that risk of

cognitive impairment is explained by multiple pathways along the life course. In this section, we discuss the three possible mechanistic pathways through which ADI may be associated with cognitive and AD/ADRD outcomes – (i) lower AD pathology [also termed as "Resistance" (Arenaza-Urquijo and Vemuri, 2018) where lower than expected AD pathology is observed]; (ii) better brain health (Stern et al., 2018); (iii) higher cognitive reserve (Stern et al., 2018). We discuss the latter two pathways in the context of "Resilience" to AD pathologies wherein some individuals cope with pathologies better than others. Here we highlight literature where mediators (identified in **Figure 1**) have been shown to impact risk of cognitive impairment through each of these pathways.

Factors Contributing to Lower Alzheimer's Disease Pathological Burden

"Resistance to AD pathologies" has been suggested through a multitude of protective factors. While sleep has been the most consistently shown protective factor against amyloidosis through the clearance of neurotoxic waste (Spira et al., 2013; Xie et al., 2013; Carvalho et al., 2018); gene x environment interactions are also increasingly being recognized as contributors to Resistance to AD (Wirth et al., 2014; Coomans et al., 2022). Though physical and cognitive lifestyle has been proposed to influence AD pathological burden (Landau et al., 2012; Okonkwo et al., 2014), these findings have not been consistent across studies. Because ADI reflects several of these mediator factors, one would expect a relationship between ADI and AD neuropathology. A recent study found evidence for this association by suggesting that living in the most disadvantaged neighborhood decile was associated with more than twice the odds of Alzheimer's disease neuropathology (i.e., diffuse plaques or neuritic plaques) (Powell et al., 2020).

Factors Contributing to Better Brain Health

There are a greater number of factors that have been shown to have an impact on brain health (which reflects overall brain structure and function and commonly measured using MRI and FDG-PET). Comorbidities, that could be more prevalent in persons with higher neighborhood socioeconomic deprivation or high ADI, have been found consistently to be associated with greater neurodegeneration independent of amyloidosis (Vassilaki et al., 2016; Vemuri et al., 2017). Even in midlife before the onset of neurodegenerative pathologies, poor general health status was associated with worse brain health (Neth et al., 2019). Overall general health is greatly influenced by several upstream processes such as cognitive activity, physical activity, lifestyle, education, and occupation. Several of these mediating factors have a bidirectional relationship with neighborhood disadvantage. A review provided evidence that socioeconomic status (SES) is associated with developmental trajectories of gray matter structure (Rakesh and Whittle, 2021). Hunt et al. (2020) found that higher socioeconomic disadvantage, as measured by ADI, was associated with lower hippocampal and total brain tissue volume, lending support for this pathway from ADI to risk of cognitive impairment.

Factors Contributing to Higher Cognitive Reserve

Cognitive Reserve refers to the property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury (Definition from the https://reserveandresilience.com/). Therefore, in addition to protective pathways through lower AD pathological burden and better brain health, lower ADI (or higher neighborhood SES) will act through the cognitive reserve pathway to reduce the risk of cognitive impairment.

Cognitive reserve is influenced by genetic and environmental exposures throughout the lifespan, which would be impacted by neighborhood socioeconomic deprivation. For example, in Apolipoprotein E ε4 carriers, years of schooling were associated with significantly delayed cognitive endpoints in patients with late-onset AD, possibly suggesting the neuroprotective effects of educational activities and their association with cognitive reserve (de Oliveira et al., 2018). We hypothesize that a rich in resources environment with opportunities for leisure and physical activities, community centers for social interactions, public libraries, and safety would promote cognitive reserve. Neighborhood SES is reflective of factors that could affect development (e.g., quality of education, access to parks and libraries or health care, crime, and pollution) (Rakesh and Whittle, 2021). An important proxy of cognitive reserve in the literature so far has been education levels, usually measured at the individual level, but also reflects access and educational opportunities of the area-level or neighborhood socioeconomic status. Children in poverty are more likely to have developmental delay, worse performance on cognitive and achievement tests than their more fortunate peers and their SES is associated with educational accomplishment, psychological welfare, and health decades later, as reviewed in Johnson et al. (2016). Socioeconomic difficulties, education in preschool years, in childhood and adolescence, and financial resources have been associated with both cognitive development and cognitive impairment in the life course (Cha et al., 2021). This evidence supports the downstream effects of the SES and ADI throughout life on cognitive reserve. In fact, in previous studies in LMICs (Mukadam et al., 2019; Ashby-Mitchell et al., 2020) low education and physical inactivity contributed to a greater fraction of dementia cases than depression and diabetes, reflecting the potential for positively impacting cognitive reserve going forward and AD/ADRD postponement and prevention in the countries that most dementia cases occur.

IMPORTANT CONSIDERATIONS AND FUTURE DIRECTIONS

Through multiple risk mechanisms (e.g., reduced educational opportunities, or access to quality medical care or healthy food, chronic stress, increased morbidity), neighborhood disadvantage can adversely impact cognitive impairment risk but be at the same

time a modifiable risk factor, amenable to policy changes that can affect communities.

Therefore, studying the broad range of factors intertwined with ADI and mechanisms through which ADI may impact cognitive outcomes is crucial. As discussed, socioeconomic conditions across the lifespan could be associated with the risk of cognitive impairment through three main pathways. Though difficult to separate both the upstream factors that emerge from worse ADI and all the mechanisms at play, ADI is very attractive as a proxy of resilience that captures multifactorial contributors to the risk of dementia. Here are some open challenges and research avenues on the horizon along with new opportunities.

Area deprivation index (Zuelsdorff et al., 2020) is a validated composite measure of neighborhood disadvantage, funded by the National Institutes of Health and publicly available for the United States and Puerto Rico through the Neighborhood Atlas® (Kind and Buckingham, 2018). Thus, the research community can easily incorporate ADI in their studies and assess disparities in brain resilience and area-level socioeconomic deprivation. As suggested by the National Institute on Aging Health Disparities Research Framework, the socioeconomically disadvantaged populations are included in the priority populations for health disparities in aging research (Hill et al., 2015; National Institute on Aging, 2022). In addition, the Neighborhood Atlas® provides ADI ranking within a state and nationally, allowing further comparisons between studies within a state or nationwide.

The life course approach suggests that health is influenced by past exposures even decades earlier (Jones et al., 2019). Resilience in dementia and aging is a process developed over the lifespan, while lifetime exposures interact and accumulate, resulting in chronic diseases (Lynch and Smith, 2005; Arenaza-Urquijo and Vemuri, 2020). However, few studies have recreated the area-level socioeconomic deprivation in the lifespan to examine its association with cognitive impairment (George et al., 2020). A life-course approach could allow the study of SES exposures during gestation and the different life epochs (i.e., childhood, young adulthood, midlife, older adulthood), that accrue and interact over the years to modify resilience and cognitive impairment risk (Kuh et al., 2003; George et al., 2020). Such studies would assist in the identification of Resilience area-level SES markers across the lifespan and possibly specific most vulnerable life epochs, which is also important in understanding mechanisms of action.

Changes in cognition associated with neighborhood characteristics (e.g., available resources like proximity to public transport or community centers) appear to be lesser than changes related to one's health behaviors; however, beneficial changes in neighborhood deprivation could be easier to implement than changing an individual's health behaviors in a deprived area (Clarke et al., 2015). Thus similarly, it might be easier to build, preserve or improve brain resilience in an environment that facilitates instead of hindering physical, social, and cognitively beneficial activities. This is especially important, as postponing dementia onset by even 1 year could result in nine million fewer cases worldwide than predicted by 2050 (Brookmeyer et al., 2007).

AUTHOR CONTRIBUTIONS

PV conceived the idea. PV and MV equally contributed to drafting the manuscript. RP provided critical review and input. All authors contributed to the article and approved the submitted version.

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Musical Activity During Life Is Associated With Multi-Domain Cognitive and Brain Benefits in Older Adults

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Regular musical activity as a complex multimodal lifestyle activity is proposed to be protective against age-related cognitive decline and Alzheimer's disease. This cross-sectional study investigated the association and interplay between musical instrument playing during life, multi-domain cognitive abilities and brain morphology in older adults (OA) from the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) study. Participants reporting having played a musical instrument across three life periods

(n = 70) were compared to controls without a history of musical instrument playing (n = 70), well-matched for reserve proxies of education, intelligence, socioeconomic status and physical activity. Participants with musical activity outperformed controls in global cognition, working memory, executive functions, language, and visuospatial abilities, with no effects seen for learning and memory. The musically active group had greater gray matter volume in the somatosensory area, but did not differ from controls in higher-order frontal, temporal, or hippocampal volumes. However, the association between gray matter volume in distributed frontal-to-temporal regions and cognitive abilities was enhanced in participants with musical activity compared to controls. We show that playing a musical instrument during life relates to better late-life cognitive abilities and greater brain capacities in OA. Musical activity may serve as a multimodal enrichment strategy that could help preserve cognitive and brain health in late life. Longitudinal and interventional studies are needed to support this notion.

Keywords: brain aging, resilience, cognitive reserve, prevention, brain plasticity, instrument playing

INTRODUCTION

Given that world populations are aging, age-related diseases such as Alzheimer's disease (AD) are on the rise and pose public health challenges of utmost importance (Alzheimer's Association, 2021). Healthy lifestyle activities are proposed to enhance brain and cognitive resources in older adults (OA) (Valenzuela et al., 2012; Wirth et al., 2014; Arenaza-Urquijo et al., 2015; Livingston et al., 2020), which may strengthen resilience against cognitive decline in aging and AD. Among others, regular musical activity, such as playing a musical instrument, is associated with reduced risk of developing dementia (Verghese et al., 2003; Balbag et al., 2014). To advance targeted intervention strategies, it is important to delineate presumed cognitive benefits and underlying brain correlates associated with musical activity in older age.

It has been proposed that musical activity shares communalities with the concept of environmental enrichment (Fauvel et al., 2014b; Sihvonen et al., 2017). In animal models, far-reaching neurobiological and behavioral benefits of environmental enrichment have been shown (Kempermann, 2019a). Playing a musical instrument is a highly stimulating activity that inherently combines complex stimulations involving the simultaneous perception and integration of multimodal motor, sensory, cognitive, emotional, and social stimulations (Lappe et al., 2008). Active engagement in this multimodal leisure activity is thus proposed to facilitate beneficial brain and cognitive plasticity throughout life until old age (Wan and Schlaug, 2010).

Indeed, there is evidence to suggest that musical activity may preserve or even enhance cognitive abilities that decline in older age (Román-Caballero et al., 2018; Sutcliffe et al., 2020). For example, it has been shown that OA with musical activity (both professionals and/or amateurs) outperform controls in multiple (far-transfer) cognitive domains including executive functions, attention, language, processing speed, visuospatial and/or memory abilities (Hanna-Pladdy and MacKay, 2011; Parbery-Clark et al., 2011; Hanna-Pladdy and Gajewski, 2012; Gooding et al., 2014; Mansens et al., 2018; Strong and Mast, 2019; Gray and Gow, 2020). Moreover, some of these cognitive benefits, in particular processing speed, appear to be particularly pronounced in older participants playing a musical instrument as compared to singing (Mansens et al., 2018). While most of the existing studies are cross-sectional in nature, presumed cognitive benefits of musical activity in older age are supported by musical intervention/training studies. According to such studies in musically non-experienced OA, learning how to play a musical instrument has a robust positive impact on higher-order cognitive abilities including executive functions, working memory, speech perception and visual memory compared to control conditions (Bugos et al., 2007; Seinfeld et al., 2013; Degé and Kerkovius, 2018; Worschech et al., 2021).

Comparatively little is known about the neural underpinnings of musical activity in OA (Schneider et al., 2019). Both, cross-sectional and longitudinal studies have mainly investigated respective brain correlates in young and middle-aged participants with musical activity (both professionals and amateurs) compared to controls. In this population, musical activity seems to be associated with brain plasticity, as e.g., reflected by greater gray matter volume (GMV) as well as white matter (WM) integrity in dedicated brain regions (Wan and Schlaug, 2010; Herholz and Zatorre, 2012). Among others, these areas comprise frontal and temporal GM and WM structures (Sluming et al., 2002; Gaser and Schlaug, 2003; Halwani et al., 2011; Gärtner et al., 2013; Fauvel et al., 2014a; Groussard et al., 2014; James et al., 2014), which are also strongly affected by healthy and pathological aging (Jack et al., 1997; Habes et al., 2016; Wirth et al., 2018). Musical activity is further positively associated with hippocampal structure and function in younger musicians (professionals and/or amateurs) based on cross-sectional (Groussard et al., 2010, 2014; Oechslin et al., 2013) and intervention/training (Herdener et al., 2010) studies.

In the same line, sparse investigations are suggestive of beneficial brain–behavior relationships relating greater GM and WM integrity to musical activity in OA. Higher levels of musical activity are correlated with larger GMV in frontal (inferior) and temporal (parahippocampal) brain regions in OA with various

musical experiences (Chaddock-Heyman et al., 2021). Moreover, larger GMV in frontal (inferior) and temporal (hippocampal and superior temporal) regions has been found in a lifespan sample of professional piano tuners compared to controls (Teki et al., 2012). Another study showed greater WM microstructural integrity in the superior longitudinal fasciculus and uncinate fasciculus in aging musicians (Andrews et al., 2021). Finally, recent intervention/training studies in musically non-experienced OA have reported enhanced neural efficiency in a distributed frontal, temporal, and parietal network (Guo et al., 2021), stabilized WM microstructural integrity in the fornix (Jünemann et al., 2022) and increased cortical thickness in auditory brain regions (Worschech et al., 2022) in response to musical instrument playing compared to control conditions.

The main goal of the present cross-sectional study was to shed light on the association between participating in musical activity and indicators of brain and cognitive health in OA. Existing findings propose that regular musical activity, in particular playing a musical instrument (Mansens et al., 2018), may have benefits for late-life cognitive abilities. There is further indication that musical activity is associated with neurophysiological correlates of cognitive reserve and/or brain reserve in older age (Sutcliffe et al., 2020). Together, these mechanisms could contribute to better cognitive abilities (Chaddock-Heyman et al., 2021) and help counteract brain pathology (Stern et al., 2020) in late life, warranting further investigations. Here, we combined measures of long-term musical activity (as assessed by the self-reported frequency of playing a musical instrument across three life periods), multi-domain cognitive abilities and regional brain morphology to investigate the association and interplay among these variables in cognitively unimpaired OA. We hypothesized that musical activity is associated with better late-life abilities in multiple cognitive domains as well as larger GMV in pre-selected frontal, temporal and hippocampal regions and at the voxel level. We further anticipated that musical activity could be associated with a more efficient use of structural brain capacities, which may convey resilience in late life.

MATERIALS AND METHODS

Overall Study Approach

To address our research questions, the present study assembled data from the ongoing, multi-center, observational DZNE-Longitudinal Cognitive Impairment and Dementia (DELCODE) study (Jessen et al., 2018) using a unique methodological approach: (1) Musical activity was assessed in a large sample of cognitively unimpaired OA (aged $\geq$ 60 years) as a binary group variable (i.e., participants with musical activity and well-matched controls) based on the self-reported frequency of playing a musical instrument across three life periods (i.e., young adulthood, mid-life, and late-life). (2) Cognitive abilities were assessed using sensitive latent factor composite scores across five cognitive domains and a global cognitive score (Wolfsgruber et al., 2020). (3) Brain morphology was assessed within pre-selected regions-of-interest (ROI) and at the voxel level to identify the spatial pattern of GMV associated with musical activity. (4) We accounted for reserve proxies (Stern, 2009) of high educational attainment, crystallized intelligence, socioeconomic status (SES) and participation in physical activity, most of which were considered in earlier studies on musical activity and cognitive abilities (Hanna-Pladdy and MacKay, 2011; Gooding et al., 2014; Mansens et al., 2018; Gray and Gow, 2020). In addition, we controlled for these potential confounders in respective associations with brain morphology.

Participants

The sample used in the present study was obtained from the baseline DELCODE study. The overall design of the DELCODE study is explained in the supplement. In the present study, cognitively unimpaired participants, i.e., OA, first-degree relatives of AD patients (family history, FH), and participants with subjective cognitive decline (SCD), were included and merged across the three groups to increase the final sample size and statistical power. Recruitment procedures and inclusion criteria are described in detail elsewhere (Jessen et al., 2018). In brief, all participants were aged $\geq$ 60 years, German speaking, and provided informed consent. Normal cognitive function was defined as a test performance within −1.5 standard deviations of age-, sex- and education-adjusted norms on all subtests of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) test battery (Morris et al., 1989). Exclusion criteria for OA, FH, and SCD were comprised of medical conditions including current or past major medical, neurological, or psychiatric disorders.

The DELCODE baseline dataset (total: n = 1079, data release for this study: 01.2021) was used to select a subset of participants into the present study. The selection procedure is detailed in the supplement (**Supplementary Figure 1**). We were able to include n = 70 older participants that reported musical activity across the life course (group of interest) and a well-matched control group (n = 70, for methodological details see below).

Measurements

Measurement of Musical Activity

We operationalized musical activity by the self-reported frequency of playing a musical instrument across three life periods ranging from young adulthood (13 30 years), mid-life (30–65 years) to late-life (65 years onwards). The approach was chosen, because participation in musical activity across the life course might be particularly beneficial with brain plasticity thought to continue throughout life (Wan and Schlaug, 2010). In agreement with a previous large-scale population study (Mansens et al., 2018), we used the available self-reported information to assess participation in musical activity. In the DELCODE cohort, musical activity was measured with the Lifetime of Experiences Questionnaire (LEQ, Valenzuela and Sachdev, 2007) adapted for the German population (Roeske et al., 2018). Details on the quantification and analysis of musical activity are provided in the supplement.

In brief, for each life period, the frequency of musical activity was measured using the respective LEQ item ("How often did you play a musical instrument?") with responses provided on a 6-point Likert scale (0/'never,' 1/'less than 1 time per month,' 2/'1 time per month,' 3/'2 times per month,' 4/'weekly,' 5/'daily'). We constructed a coding scheme to assess musical activity during life

as a binary variable that was comprised of two groups, similar to the previous study (Mansens et al., 2018): (1) The musical activity group (group of interest) included participants that reported having played a musical instrument during life. All participants started in early adulthood and continued playing until the current life period with higher frequency ('2 times per month' or more) in at least one life period, given their respective age. Notably, a total of n = 67 started playing a musical instrument with higher frequency in young adulthood, n = 47 played a musical instrument with higher frequency in at least two life periods and n = 23 played a musical instrument with higher frequency in one life period. A detailed graphical description showing the individual trajectories of musical activity across the given life periods is provided in the supplement (**Supplementary Figure 2**). (2) The control group included participants that reported to never have played a musical instrument in any of the given life periods.

Measurement of Cognitive Abilities

Cognitive abilities were assessed using latent composite scores of five cognitive domains, namely (1) learning and memory, (2) working memory, (3) executive functions and mental processing speed, (4) language, and (5) visuospatial abilities and a global cognitive score (i.e., the mean across the five cognitive domains). The composite scores were created by using a confirmatory factor analysis on neurocognitive tests from the extensive neuropsychological test battery in the DELCODE cohort, as described (Wolfsgruber et al., 2020) and applied (e.g., Amaefule et al., 2021; Ballarini et al., 2021; Wesselman et al., 2021) in previous reports. Information on the methodological procedure are provided in the supplement. Notably, the construction of latent factors scores across multiple neuropsychological tests is an established procedure (Hedden et al., 2012; Benson et al., 2018) with several advantages (Gross et al., 2015): Each latent factor represents a construct measured by the shared variance across multiple indicator variables. Thus, the latent variables are adjusted for measurement error and specificities of the individual tests. The method allows for an objective evaluation of cognitive performance across multiple tests and results can be generalized above the specific measurement methods.

The following neuropsychological tests contributed to each cognitive domain: (1) Learning and memory: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) word list: trial 1, 2, 3, delayed recall and recognition, Free and Cued Selective Reminding Test (FCSRT) free recall and cue efficiency, Wechsler Memory Scale (WMS) logical memory 1 and 2, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) figure savings, Symbol-Digit-Modalities Test (SDMT) incidental learning, Face Name Test. (2) Working memory: Digit Span Forward and Backward, FCSRT interference task (Serial 3 s). (3) Executive functions: Trail Making Test (TMT) A and B, Number Cancelation, SDMT, Flanker Task. (4) Language: verbal fluency groceries and animals, Boston Naming Test (20 items), FCSRT naming. (5) Visuospatial abilities: Clock copying and drawing, CERAD Figure copying. Each cognitive composite score was z-transformed using the here-selected DELCODE baseline sample.

MRI Acquisition and Processing

The MRI data were acquired using 3-Tesla MRI scanners (Siemens, Erlangen, Germany), including three TIM Trio systems, four Verio systems, one Skyra system, and one Prisma system. The extensive MRI protocol of the DELCODE study is described elsewhere (Jessen et al., 2018). For the present analysis, we used T1-weighted images (i.e., 3D GRAPPA PAT 2, 1 mm^3 isotropic, 256 × 256 px, 192 slices, sagittal, ∼ 5 min, TR 2500 ms, TE 4.33 ms, TI 110 ms, FA 7°) and T2-weighted images (i.e., 0.5 × 0.5 × 1.5 mm^3, 384 × 384 px, 64 slices, orthogonal to hippocampal long axis, ∼12 min, TR 3500 ms, TE 353 ms, optimized for volumetric assessment of the medial temporal lobe). All scans underwent quality assessment provided by the DZNE imaging network (iNET, Magdeburg).

Regional GMV analysis was conducted in pre-selected ROI robustly affected by healthy and pathological aging due to AD. Based on prior findings (Jack et al., 1997; Habes et al., 2016; Wirth et al., 2018), we chose three ROIs comprising the frontal lobe, the temporal lobe and the hippocampus. Cortical GMV was evaluated as a global measure of brain integrity. For each of the ROIs, we used regional GMV measures provided in the DELCODE database, as described previously (Düzel et al., 2018). In brief, structural MRI images were segmented in native space using an automated cortical parcellation pipeline (Fischl et al., 2004) implemented in FreeSurfer[1] (version 6.0) and an advanced segmentation tool (Iglesias et al., 2015) to derive ROI-based GMV measures. Frontal and temporal GMV were calculated as the sum over selected ROIs of the left and right hemisphere, as proposed by Desikan et al. (2006). Left and right hippocampal volume were summed as a measure of the overall hippocampal volume. Details on the ROI computation are provided in the supplement. Regional GMV measures were adjusted for total intracranial volume (TIV), as estimated using FreeSurfer (Buckner et al., 2004).

We further assessed GMV at the voxel level using the following procedure. Structural MRI images were segmented to extract gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissues using the unified segmentation algorithm in CAT12[2] (version 12.6) with default parameters. Warping to the Montreal Neurological Institute (MNI) template space was performed using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) with default parameters and registration to existing templates (Ashburner, 2007). TIV was computed as the sum of volumes of GM, WM, and CSF using the SPM "Estimate TIV and global tissue volumes" routine. Voxel-based statistical analyses were performed on the warped and modulated GMV maps, which were smoothed by a three-dimensional Gaussian kernel with full width at half maximum of 8 mm^3.

Additional Measures

Age, sex, education, diagnostic category and known reserve proxies of crystallized intelligence, SES, and self-reported participation in physical activity were considered as potential

[1] http://surfer.nmr.mgh.harvard.edu/

[2] http://dbm.neuro.uni-jena.de/vbm

confounders. Educational attainment was measured in years of education. Crystallized intelligence was estimated using the Multiple-Choice Vocabulary Intelligence Test (MWT, min. score: 0, max. score: 37), with higher scores being proportionally related to a higher level of verbal intelligence (Lehrl, 2005). The MWT is considered an established tool for the assessment of crystallized intelligence. The SES was estimated for each participant using the international socio-economic index of occupational information score (ISEI, min. score: 16, max. score: 90) (Ganzeboom et al., 1992), based on the occupational history assessed by the LEQ. Details on the SES computation are provided in the supplement.

Participation in physical activity (long-term and current) was assessed using the respective items of the LEQ and the Physical Activity Scale for the Elderly (PASE, min. score: 0) (Washburn et al., 1999), respectively. Self-reported participation in long-term physical activity was measured based on LEQ responses on the frequency of physical activity recorded for each life period using the 6-point Likert scale (see above). A mean score was calculated over the available participant's responses including at least two life periods. In addition, current physical activity was assessed through the Physical Activity Scale for the Elderly (PASE, min. score: 0) (Washburn et al., 1999). The PASE includes leisure, household and occupational activities measured over the previous week. Based on frequency, duration, and intensity of these activities, a total score is calculated with higher scores indicating greater levels of physical activity. Long-term physical activity was significantly correlated with current physical activity in the matched sample ($n = 140$, $r = 0.35$, $p < 0.001$), supporting the validity of the measure. Long-term physical activity was used as a covariate in statistical analyses, since the measure was available from all participants.

Statistical Analyses

Statistical analyses were conducted using *R* (version 3.5.1.) and Statistical Parametric Mapping (SPM, version 12, Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Figures were generated using the package *ggplot2* (Wickham, 2016). Before conducting statistical models, statistical assumptions were assessed visually using diagnostic plots.

Sample Characteristics

Participants reporting musical activity during life and controls with no musical activity were matched using a one-to-one matching procedure taking into account age, sex, diagnostic category, education, SES, crystallized intelligence, and long-term physical activity. Further details are provided in the supplement including sample descriptive of the pre-matching sample (**Supplementary Table 1**). The one-to-one matching procedure was carried out using propensity score matching with the *R* package *MatchIt* (version 4.1.0.) (Ho et al., 2011). This statistical matching technique aims to estimate treatment or intervention effects by accounting for several covariates. Observations were matched based on the nearest-neighbor method, as a simple and effective procedure for selecting well-matched groups (Stuart, 2010). After matching, musical activity groups were compared in baseline demographic, behavioral, neuropsychological, and neuroimaging variables. Independent Student's *t*-tests were used for all continuous variable and chi-squared (χ^2) tests were applied for all categorical variables.

Regions-of-Interest-Based Analyses

Multiple linear regression models were used to assess our main hypotheses. In these statistical analyses, an alpha value of 0.05 was considered statistically significant. In addition, correction for multiple comparisons was performed using a false discovery rate (FDR)-adjusted *p*-value threshold (alpha) of 0.05 (Benjamini and Hochberg, 1995). Uncorrected *p*-values were reported, when results survived FDR correction, this is highlighted in respective result tables.

Firstly, the association between the musical activity groups (modeled as a main effect) and cognitive abilities were assessed using the cognitive composite scores. Multiple linear regression models were computed including musical activity (binary group) as an independent variable and each cognitive composite score (*z*-transformed) as a dependent variable, respectively. Next, the association between musical activity and brain morphology was examined using similar multiple linear regressions. The models included musical activity (binary group) as independent variable and each ROI-based GMV (frontal, temporal and hippocampus, all TIV adjusted) as dependent variable along with scanner site as covariate (dummy coded). Selected associations were visualized to facilitate the interpretation of findings using box plots of unadjusted data.

Next, we assessed the moderation of musical activity on the association between ROI-based GMV and cognitive abilities. To do this, musical activity (binary group), ROI-based GMV (frontal, temporal, and hippocampal, all mean-centered), and the interaction (musical activity × ROI-based GMV) along with scanner site as covariate (dummy coded) were entered into multiple regression models with each cognitive composite score (*z*-transformed) as dependent variable. To specify the directionality of significant interactions, simple slope analyses were carried out (Aiken and West, 1991; Cohen et al., 2003). Moderation effects were visualized using unadjusted data as follows: cognitive composite scores (*z*-transformed) were graphed as a function of musical activity and ROI-based GMV, respectively.

Voxel-Based Analysis

To elucidate the spatial distribution of the associations between musical activity and brain morphology at the voxel level, multiple linear regressions were computed in SPM12. For the present purpose, voxel-wise results were presented at $p < 0.001$ uncorrected and, if applicable, $p < 0.05$ with family-wise error (FWE) correction at peak level, in combination with the estimated expected voxels per cluster (k), as automatically calculated by SPM.

First, a multiple regression model was computed with musical activity (binary group) as independent variable and the modulated, warped, and smoothed GMV maps as dependent variable. Next, a moderation of musical activity was evaluated at the voxel level. This multiple regression model included musical activity (binary group), the respective cognitive composite score (*z*-transformed), and the interaction term (musical

activity × cognitive composite score) as independent variables with GMV maps as dependent variable. The later analysis was carried out for global cognition and all cognitive domains. For reasons of simplicity, results of this analysis were displayed for one cognitive domain (i.e., with the largest effect size), as selected by the strongest moderation effect in the ROI-based analysis. Additional findings were provided in the extended data documentation.

All voxel-based analyses were adjusted for TIV as well as scanner site (dummy coded) and restricted to cerebral GM using an explicit binary GM mask derived from the present sample (i.e., average GM map thresholded at a level of > 0.3, excluding cerebellum and brain stem). Cluster peaks are specified by anatomical site, as labeled using the Hammersmith atlas (Hammers et al., 2003) provided by the CAT12 toolbox. Additionally, Brodmann areas (BA) were identified for cluster peaks using the BioImage Suite Web 1.2.0[3] (GitHub, Retrieved December 2, 2021). Finally, mean values were extracted for each participant within combined clusters using the warped, modulated, and non-smoothed GMV images using the MarsBaR toolbox (release: 0.44[4]) (Brett et al., 2002), to provide complementary visualizations of the associations.

RESULTS

Sample Characteristics

This study included a total sample of 140 older participants (aged ≥ 60 years) selected from the DELCODE cohort. The present sample comprised 70 participants reporting participation in musical activity during life and 70 well-matched controls without musical activity. The two groups (musical activity, no musical activity) were comparable in age, sex, distribution of diagnostic categories as well as reserve proxies including higher educational attainment, crystallized intelligence, SES, and participation in both long-term and current physical activity (all *p's* > 0.05, **Table 1**). Slight group differences in frontal and total GMV (unadjusted raw values) were observed, with larger volumes in the older participants with musical activity compared to controls. No significant differences were observed in the temporal and hippocampal GMV (unadjusted raw values).

Musical Activity and Cognitive Abilities

First, we assessed the association between musical activity and cognitive abilities using the latent composite scores. We found significant group differences for global cognition, working memory, executive function, language and visuospatial abilities (all *p's* < 0.05, **Table 2** and **Figure 1**). Performance in these cognitive abilities was significantly better in participants with musical activity compared to controls. In contrast, the two groups did not differ significantly the domain of learning and memory ($p = 0.209$).

[3]https://github.com/bioimagesuiteweb/bisweb

[4]http://marsbar.sourceforge.net/

Musical Activity and Brain Morphology in Regions-of-Interest

Second, we assessed the association between musical activity and regional GMV in pre-selected frontal, temporal and hippocampal ROIs (TIV-adjusted values). There were no significant group differences between participants with musical activity compared to controls in frontal ($p = 0.822$), temporal ($p = 0.711$), and hippocampal ($p = 0.551$) GMVs. Furthermore, the two groups did not differ significantly in total cortical GMV ($p = 0.722$). Results are shown in **Table 3**. In a *post hoc* analysis, the association between musical activity and frontal, temporal and hippocampal ROIs was analyzed separately for left and right hemispheres. There were no significant differences in the ROI-based GMVs between participants with musical activity and controls (all *p's* > 0.1, **Supplementary Table 2**).

Moderations of Musical Activity in Regions-of-Interest

Third, a moderation of musical activity was assessed by the interaction between musical activity and GMV in the frontal, temporal and hippocampal ROIs, respectively. We found overall positive associations of frontal GMV with global and domain-specific cognitive abilities (all *p's* ≤ 0.01, data not shown). Importantly, musical activity interacted with frontal GMV for global cognition, working memory, and language abilities (all *p's* < 0.05; **Table 4**). Visualization of this moderation effect (**Figure 2**) showed that the association between frontal GMV and those cognitive abilities was enhanced in participants with musical activity compared to controls. That is, larger frontal GMV was significantly associated with better cognitive abilities in the participants with musical activity (all *p's* < 0.05, **Figure 2**). The moderation effect was not detectable for the domain of learning and memory ($p = 0.441$).

For the temporal and hippocampal ROIs, we found overall positive associations of temporal GMV with global and domain-specific cognitive abilities (all *p*'s < 0.01, data not shown). For the temporal ROI, we detected a moderation of musical activity on the association of temporal GMV and global cognition, working memory and language abilities (all *p's* < 0.05 uncorrected, **Supplementary Table 3**). There was no significant moderation of musical activity on the association between hippocampal GMV and cognitive abilities (all *p's* > 0.1, **Supplementary Table 4**).

Voxel-Based Analysis

Our analysis at the voxel level largely confirmed the ROI-based findings. Regarding the main effect, there was a subtle positive association between musical activity and local GMV within a small cluster in the left postcentral gyrus ($p < 0.001$ uncorrected; **Table 5** and **Figures 3A,B**). No other significant clusters were found. When investigating the moderation of musical activity at the voxel level, significant clusters of regional GMV were detected in prefrontal (lateral and medial), inferior temporal, and precentral regions ($p < 0.001$ uncorrected; **Table 5**). Visualization

TABLE 1 | Descriptive characteristics of the matched DELCODE sample (n = 140).

	Musical activity	No musical activity	*P*-value
Number (*n*)	70	70	–
Age (years)	68.23 (6.62)	69.01 (5.44)	0.445
Gender female/male (*n*)	31/39	35/35	0.498
Education (years)	16.20 (2.71)	15.96 (2.74)	0.598
Diagnostic category OA/FH/SCD (n)	19/7/44	24/6/40	0.654
SES[a]	66.27 (16.32)	65.21 (16.04)	0.699
Crystalized intelligence[b]	33.31 (2.14)	33.04 (2.22)	0.463
Physical activity, long-term[c]	4.25 (0.78)	4.32 (0.71)	0.611
Physical activity, current[d]	33.86 (11.80), *n* = 66	32.45 (12.85), *n* = 69	0.507
Total frontal GMV (ml)	138.86 (12.44)	134.69 (11.88)	0.044*
Total temporal GMV (ml)	95.53 (8.44)	93.29 (8.3)	0.115
Total hippocampal GMV (ml)	6.26 (0.71)	6.21 (0.66)	0.692
Total cortical GMV (ml)	453.83 (37.56)	441.69 (37.13)	0.049*

*Descriptive data are given if applicable as mean and standard deviation (in parenthesis). The actual sample size is provided, if different from sample size specified in first row. P-values correspond to independent t-tests for unequal variance with participant group as independent variable. Chi-square statistic was used to compare the distribution of categorical variables. *$p < 0.05$. OA, older adults; FH, participants with a family history of AD; GMV, gray matter volume; SCD, participants with subjective cognitive decline; SES, socioeconomic status.*

[a]International socio-economic index (ISEI); [b]Multiple-Choice Vocabulary Intelligence Test (MWT); [c]Lifetime of Experiences Questionnaire (LEQ); [d]Physical Activity Scale for the Elderly (PASE).

PASE: The total score was calculated based on frequency, duration, and intensity of leisure, household and occupational activities. Higher scores correspond to greater levels of physical activity.

LEQ: The mean frequency of physical activity over available life periods was measured using a 6-point Likert scale (0 = 'never,' 1 = 'less than 1 time per month,' 2 = '1 time per month,' 3 = '2 times per month,' 4 = 'weekly,' 5 = 'daily'). Higher scores correspond to greater frequencies of physical activity.

TABLE 2 | Results of linear regression analyses between musical activity and cognition.

	Dependent variable	Independent variable	*B*	SE B	Beta	*P*-value	Total R^2 (adj.)
1	Global cognition	Musical Activity	0.540	0.178	0.250	0.003**†	0.062 (0.056)
2	Learning and Memory	Musical Activity	0.209	0.165	0.107	0.209	0.011 (0.004)
3	Working Memory	Musical Activity	0.669	0.178	0.304	<0.001***†	0.092 (0.086)
4	Executive Functions	Musical Activity	0.465	0.180	0.214	0.011*†	0.046 (0.039)
5	Language	Musical Activity	0.443	0.170	0.216	0.010*†	0.047 (0.040)
6	Visuospatial	Musical Activity	0.522	0.176	0.245	0.003**†	0.060 (0.053)

*Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. †$p < 0.05$ false discovery rate (FDR)-adjusted for statistical tests performed across cognitive domains. B, unstandardized coefficient; SE, standard error; Beta, standardized coefficient; R^2, explained variance.*

of this moderation effect for working memory (i.e., domain with the largest effect size) indicated that larger GMV was associated with better working memory ability only in participants with musical activity (**Figures 3C,D**). Overall, the results of the voxel-wise moderation analysis across all cognitive composites were essentially similar, with some variations in the number and location of significant clusters (**Supplementary Table 5** and **Supplementary Figure 3**).

DISCUSSION

Summary of Findings

The current study examined cognitive abilities, brain morphology, and their interplay in OA that reported having played a musical instrument across three life periods. Participants with a history of long-term musical activity were compared to controls (i.e., without a history of musical instrument playing) that were closely matched for known reserve proxies. We document three main findings: (1) Participants with musical activity outperformed controls in global and multi-domain cognitive abilities, but not in learning and memory. (2) Participants with musical activity did not significantly differ from controls in GMV within the higher-order frontal, temporal, and hippocampal regions. (3) The association between GMV in distributed frontal-to-temporal regions and multi-domain cognitive abilities was enhanced in participants with musical activity compared to controls. Together, our correlational findings suggest that participation in musical activity during life is associated with brain and cognitive benefits in late life and could strengthen cognitive resilience. Longitudinal studies are needed to support this interpretation.

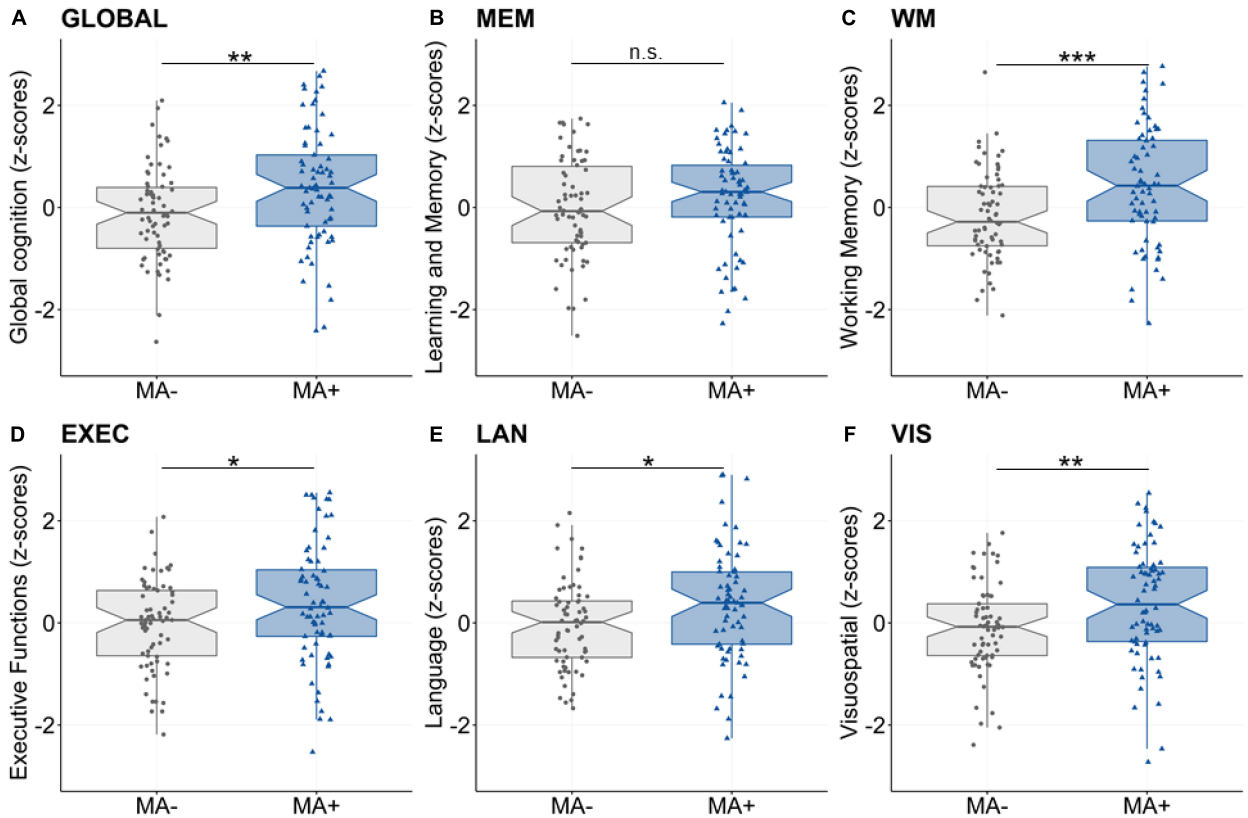

FIGURE 1 | Main effect of musical activity on multi-domain cognitive abilities. Significant group differences were found for global cognition (**A**, GLOBAL), working memory (**C**, WM), executive function (**D**, EXEC), language (**E**, LAN), and visuospatial abilities (**F**, VIS). These multi-domain cognitive abilities were enhanced for participants with musical activity (MA+, blue) compared to controls (no musical activity across lifespan, MA-, gray). The association was not significant for the learning and memory composite (**B**, MEM). Boxplots display unadjusted data with individual data points. The "notch" shows the median with 95% confidence intervals and interquartile range with lower (25th) and upper percentiles (75th). Significance levels (uncorrected): ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. MA+, musical activity; MA–, no musical activity.

Musical Activity and Cognitive Abilities

We show that musical activity during life is associated with better late-life cognitive abilities in OA. More precisely, participants with musical activity outperformed the matched controls in global cognition and multiple cognitive domains including working memory, executive functions, language and visuospatial abilities. These findings agree with a body of studies, suggesting that active participation in musical activity is associated with higher-order cognitive abilities in OA, based on correlational (Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012; Mansens et al., 2018; Groussard et al., 2020) and intervention/training (Bugos et al., 2007; Seinfeld et al., 2013; Worschech et al., 2021) studies. A recent meta-analysis of active musical training further demonstrates a small but measurable benefit of this leisure-time activity on cognitive functioning in OA with mild cognitive impairment and dementia (Dorris et al., 2021).

In our study, the association between musical activity and late-life cognitive abilities was greatest for working memory ($\beta = 0.304$), a fundamental cognitive domain that is central to overall cognitive functioning (Baddeley, 2003). The result mirrors existing findings in younger (Talamini et al., 2017) and in older (Hanna-Pladdy and Gajewski, 2012; Grassi et al., 2017; Mansens et al., 2018) musically active adults and corroborates a particular involvement of frontal-lobe functions in playing music (Jäncke, 2013; Sutcliffe et al., 2020). In contrast, participants with musical activity did not differ from controls in the domain of learning and memory, although this must be perceived as an essential cognitive skill involved in playing a musical instrument (Talamini et al., 2017). Some correlational studies have reported that musical activity is indeed associated with better episodic memory in OA (Hanna-Pladdy and MacKay, 2011; Gooding et al., 2014; Mansens et al., 2018; Romeiser et al., 2021), while others do not find such effects (Hanna-Pladdy and Gajewski, 2012; Fauvel et al., 2014b; Strong and Mast, 2019). Taken together, our findings in OA substantiate that musical activity may predominantly favor cognitive abilities involving the frontal lobe.

One might argue that the present null result in learning and memory could be explained by a lack in sensitivity of our composite measure. However, this latent factor score was previously shown to capture even subtle inter-individual

TABLE 3 | Results of linear regression analyses between musical activity and GMV in regions-of-interest.

	Dependent variable	Independent variable	*B*	*SE* B	Beta	*P*-value	Total R^2 (adj.)
1	Frontal GMV	Musical Activity	–0.046	0.204	–0.020	0.822	0.120 (0.052)
2	Temporal GMV	Musical Activity	–0.053	0.142	–0.032	0.711	0.123 (0.055)
3	Hpc GMV	Musical Activity	–0.007	0.012	–0.052	0.551	0.102 (0.032)
4	Cortical GMV	Musical Activity	–0.303	0.850	–0.031	0.722	0.132 (0.065)

Models adjusted for scanner site. Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0. Regional GMV was adjusted by total intracranial volume (TIV). B, unstandardized coefficient; Hpc, Hippocampus; SE, standard error; Beta, standardized coefficient; R^2, explained variance; GMV, gray matter volume.

TABLE 4 | Results of the moderation analyses between musical activity and frontal GMV.

	Dependent variable	Independent variable	B	*SE* B	Beta	*P*-value	Total R^2 (adj.)
1	Global cognition	Music Activity × frontal GMV	0.318	0.139	0.261	0.024*†	0.332 (0.269)
2	Learning and Memory	Music Activity × frontal GMV	0.102	0.132	0.092	0.441	0.263 (0.193)
3	Working Memory	Music Activity × frontal GMV	0.432	0.141	0.348	0.003**†	0.335 (0.273)
4	Executive Functions	Music Activity × frontal GMV	0.278	0.145	0.228	0.058	0.273 (0.204)
5	Language	Music Activity × frontal GMV	0.316	0.133	0.274	0.019*†	0.320 (0.256)
6	Visuospatial	Music Activity × frontal GMV	0.227	0.145	0.189	0.119	0.251 (0.180)

*Models adjusted for scanner site. Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.Frontal GMV was adjusted for total intracranial volume and mean centered. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. †$p < 0.05$ false discovery rate (FDR)-adjusted for statistical tests performed across cognitive domains. B, unstandardized coefficient; SE, standard error; Beta, standardized coefficient; R^2, explained variance.*

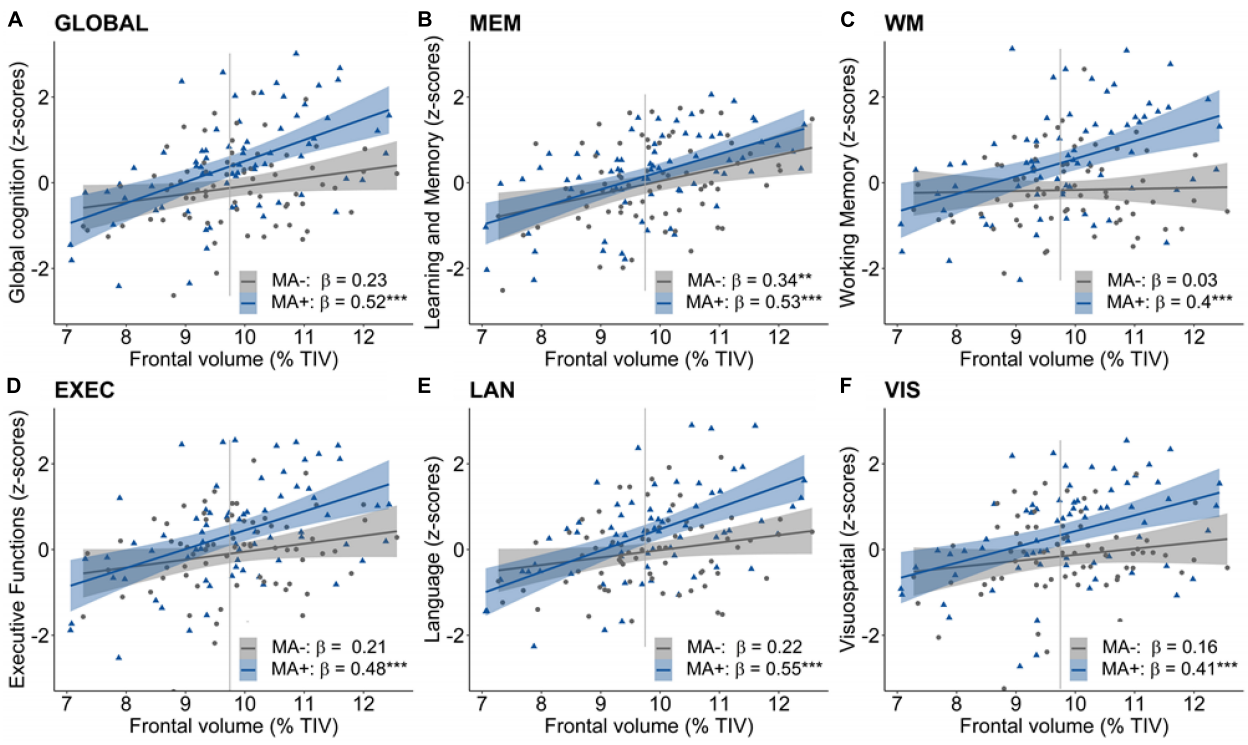

FIGURE 2 | Moderation of musical activity in the frontal region. A significant moderation of musical activity was observed for global cognition (**A**, GLOBAL), working memory (**C**, WM), and language abilities (**E**, LAN), such that larger frontal GMV was associated with better global in participants with musical activity (MA+, blue) compared to controls (MA–, gray). This interaction was not significant for learning and memory (**B**, MEM), executive functions (**D**, EXEC), and visuospatial abilities (**F**, VIS). Individual data points (dots and triangles), linear trends (solid lines), 95% confidence intervals (shaded areas), and standardized regression coefficients (β) within each group are provided. Gray vertical lines display the 90th percentile of the prefrontal GMV distribution in AD patients of the DELCODE study. Significance levels (uncorrected): ***$p < 0.001$, **$p < 0.01$. GMV, gray matter volume; MA+, musical activity; MA–, no musical activity; TIV, total intracranial volume.

TABLE 5 | Results of analyses between musical activity and GMV at the voxel level.

No. cluster	Label (Hammersmith atlas)	Brodmann area (BA)	Hemisphere	Cluster		Peak of cluster			
				P	size	*Z* value	MNI coordinates (*x y z*)		
Main effect: musical activity[a]									
1	Postcentral gyrus	BA 6	Left	0.195	220	3.60	–57	–6	27
Interaction effect[b]									
1	Precentral gyrus[†]	BA 6	Left	0.025	718	4.90	–28	–10	48
2	Precentral gyrus	BA 4	Left	0.114	322	4.81	–39	–14	33
3	Inferior middle temporal gyrus	BA 20	Right	0.054	502	4.45	51	–12	–42
4	Fusiform gyrus	BA 20	Left	0.279	145	3.99	–36	–8	–38
5	Inferior frontal gyrus	BA 46	Lateral/right	0.140	277	3.90	40	33	12
6	Anterior medial temporal lobe	BA 38	Left	0.245	168	3.78	–38	16	–36
7	Orbito-frontal lobe	BA 11	Medial/right	0.166	242	3.59	6	34	–14
8	Postcentral gyrus	BA 4	Right	0.293	137	3.52	50	–8	26

Models adjusted for scanner site and TIV.
Musical activity was included as binary predictor, dummy coded with musical activity = 1, no musical activity = 0.
[a]Results from the main effect model with musical activity and GMV ($p < 0.001$ uncorrected, expected voxels per cluster k = 140).
[b]Results from the interaction effect model with musical activity, working memory, and GMV ($p < 0.001$ uncorrected, expected voxels per cluster k = 134).
[†]Significant after FWE correction ($p < 0.05$, expected voxels per cluster k = 42).
Cluster peaks are specified by their anatomical site, labeled using the Hammersmith atlas provided by the CAT12 toolbox.
Brodmann areas were identified with the BioImage Suite Web 1.2.0.GMV, gray matter volume; MNI coordinates (x y z), coordinates in MNI space in millimeters; TIV, total intracranial volume.

differences in memory performance of OA (Wolfsgruber et al., 2020). Alternatively, it is plausible that specific memory sub-processes are enhanced by musical/auditory expertise involving the tonal stimulus modality (Talamini et al., 2017), such as long-term musical memory (Groussard et al., 2010) or auditory navigation (Teki et al., 2012), which are not mapped by our memory composite score. Experimental, neuroimaging, and neuropsychological markers tapping into more specific hippocampal processes (e.g., Stark et al., 2019) will be needed to gain further insight into presumed memory benefits associated with musical activity in older age.

Moderation of Musical Activity

As a novel finding, the present study documents a moderation of musical activity in OA. More specifically, we found that larger GMV was significantly associated with better multi-domain cognitive abilities in participants with musical activity compared to controls. This specific moderation was observed for global cognition, working memory, as well as language abilities mainly in the pre-selected frontal ROI and extended to a network of frontal, temporal and motor-sensory regions at the voxel level. A similar observation has been reported by Oechslin et al. (2013), where larger hippocampal volume was associated with better general cognitive abilities in younger musicians (professionals and amateurs), but not in non-musicians. The current study highlights that a similar association is detectable in OA with musical experience, where it is linked to distributed brain areas supporting sensory, motor and cognitive functions.

In general, the present result may reflect a more efficient use of an overall younger brain age in musically active people, as shown previously (Rogenmoser et al., 2018). Interestingly, the observed frontal-to-temporal regions partially overlap with brain networks that show enhanced functional and/or structural connectivity in young to middle-aged musicians compared to non-musicians (Halwani et al., 2011; Andrews et al., 2021; Leipold et al., 2021) and support cognitive reserve processes in older age (Colangeli et al., 2016; Marques et al., 2016; Franzmeier et al., 2017; Benson et al., 2018). In this light, our findings may imply that the long-term playing of a musical instrument could be associated with a more efficient recruitment of dedicated brain networks, as a potential benefit that might help to preserve cognitive health in late life.

Musical Activity and Brain Morphology

In our study, musical activity was not significantly associated with greater brain reserve in higher-order brain regions. More precisely, participants with musical activity did not differ from controls in GMV of the pre-selected frontal, temporal or hippocampal regions. Our voxel-based analysis largely confirmed the ROI-based observations. Merely a smaller cluster with larger GMV was found in the somatosensory area of participants with musical activity compared to controls, presumably reflecting brain plasticity in response to the intense tactile stimulations induced by playing a musical instrument (Gaser and Schlaug, 2003; Gärtner et al., 2013). Earlier studies have shown a positive association between musical activity and GMV within higher-order fontal, temporal, and also parietal regions, albeit mainly in young musician compared to controls (Gaser and Schlaug, 2003; Groussard et al., 2010; Gärtner et al., 2013) with limited evidence in OA (Chaddock-Heyman et al., 2021).

Importantly, we accounted for several reserve proxies that may help to preserve brain morphology in late life (Arenaza-Urquijo et al., 2013; Wirth et al., 2014) and thereby act as

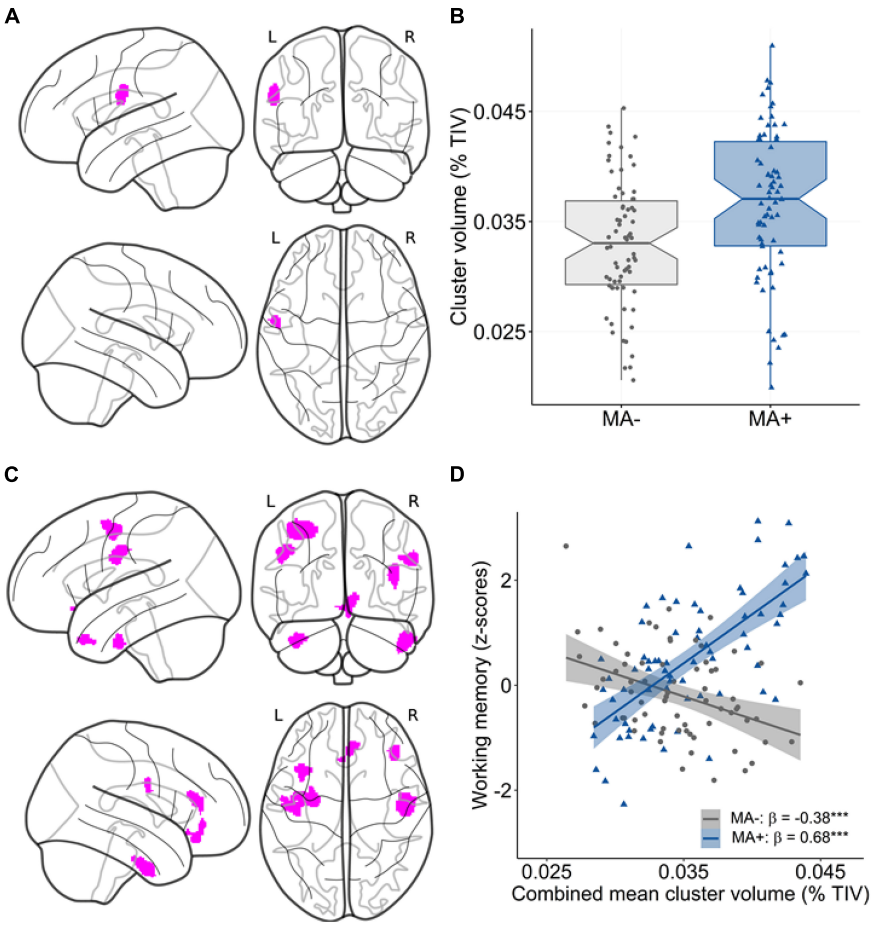

FIGURE 3 | Association between musical activity and regional volume distribution. **(A,B)** Results of the main effect analysis. Statistical map **(A)** shows significant clusters ($p < 0.001$ uncorrected, color-coded in magenta) with larger GMV in participants with musical activity compared to controls. The corresponding graph **(B)** displays the association using mean GMV values extracted from the corresponding cluster in the postcentral gyrus. The box plot displays the median with 95% confidence intervals, interquartile range with lower (25th) and upper percentiles (75th), and individual data points. **(C,D)** Results of the moderation analysis. The statistical map **(C)** displays clusters ($p < 0.001$ uncorrected, color-coded in magenta) with a significant moderation effect of musical activity. The corresponding scatter plot **(D)** shows the association using mean values extracted from the GMV maps in the combined cluster. Larger GMV in the combined cluster was associated with better working memory ability selectively in participants with musical activity (MA+, blue) compared to controls (MA–, gray). Individual data points, linear trends (solid lines), 95% confidence intervals (shaded areas), and standardized regression coefficients (β) within each musical activity group are provided. The statistical maps are depicted on a glass brain. Significance levels (uncorrected): ***$p < 0.001$. MA+, musical activity; MA–, no musical activity; GMV, gray matter volume; TIV, total intracranial volume.

potential confounders. Given this effort, it seems reasonable to assume that there is a limited added benefit of musical activity on structural brain resources (as measured using GMV) in OA within regions that are susceptible to aging and AD. Alternatively though, subtle morphological associations of musical activity could be unnoticed in the older population, due to increased morphological variability by brain aging and/or brain pathology as found in a considerable proportion of cognitively unimpaired OA (Hedden and Gabrieli, 2004; Knopman et al., 2012; Wirth et al., 2013). Lastly, it is important to note that previous cross-sectional studies reporting a positive association between musical activity and GMV in hippocampal regions as well as WM microstructural integrity included professional experts with intense musical/auditory experience (Groussard et al., 2010; Teki et al., 2012; Andrews et al., 2021). Therefore, the lack of current results with regard to a presumed modification of GMV through long-term musical activity may also have to do with the different proficiency level of our cohort.

Synopsis and Concluding Remarks

Taken together, the present study adds supportive evidence to the picture that participation in musical activity may constitute a protective factor in OA. Nevertheless, the observed health benefits associated with playing a musical instrument could be encouraged by a general engagement in an advantageous lifestyle. Those participants reporting musical activity were characterized by a high-reserve profile, including higher education, SES, crystallized intelligence, and more frequent participation in physical activity. A similar pattern was observed in previous studies (Mansens et al., 2018), but not in all (Hanna-Pladdy and

Gajewski, 2012; Gray and Gow, 2020). Together these variables may resemble a lifestyle that comprises various beneficial body and mind activities that could in synergy be associated with cognitive or brain reserve in late life (Kempermann, 2019b, 2022). Notably though, we observed superior cognitive abilities in the musically active group with those reserve proxies accounted for by our one-to-one matching procedure. This may suggest an added benefit of musical activity on late-life brain and cognitive functions. In addition, more emphasis could be placed on the assessment of a more holistic lifestyle (i.e., going beyond individual lifestyle activities) to highlight associations and presumed synergies with brain aging and reserve in future studies.

One might argue that high-functioning individuals are more likely to engage in and continue to play a musical instrument during life. In line with this argumentation, one might further expect that these high performers exhibit higher education, intelligence, and SES compared to controls. Indeed, there is confirmatory evidence to suggest that greater early-adulthood general cognitive abilities predict educational and occupational success in later adulthood (Daly et al., 2015; Kremen et al., 2019). In the present study, however, the high-functioning group was comparable to controls in the above-mentioned measures, which were deliberately accounted for when selecting the well-matched control group. Given this notion, one may reason that reverse causation seems less likely to apply to our findings, with caution that needs to be considered in correlational findings (Schellenberg, 2020).

Overall, our results converge with the view that musical activity may serve as a low-threshold multimodal enrichment strategy throughout life until old age. However, targeted intervention studies are needed to validate the impact of musical activity on late-life cognitive abilities and underlying brain correlates in OA (James et al., 2020). In light of our findings, it may be proposed that musical activity and the associated mulitmodal stimulations could strengthen cognitive resilience through benefits involving neural capacities and connections in dedicated motor-sensory-cognitive brain networks, as suggested by previous studies (Halwani et al., 2011; Andrews et al., 2021; Leipold et al., 2021). Prospective longitudinal and interventional studies must clarify whether or not musically active older people are indeed more protected against cognitive decline, which could inform targeted public health strategies.

Strengths and Limitations

Our study has several strengths. We assembled data from the observational DELCODE cohort to assess a well-characterized sample of cognitively unimpaired OA with and without self-reported participation in musical activity using cognitive, behavioral, and brain volume measures. All measures were acquired in the same participants using standardized operation procedures and high-quality data assessments. The detailed phenotyping, as provided by cohort-based studies, generated new evidence on potential brain and cognitive health benefits associated with musical activity in the older population. Moreover, we examined late-life cognitive abilities using latent factor scores, which can be generalized above the measurement method. Lastly, the availability of a wide range of variables made it possible to account for several reserve proxies, known to be enhanced in musically active older people (e.g., Mansens et al., 2018).

Several limitations need to be considered. (1) Our cohort-based approach included a limited description of musical activity/experience in the present older participants. More detailed information on lifetime musical activity including, e.g., the type of musical instrument, age of acquisition, training intensity and other musical abilities would be desirable (Okely et al., 2021), given that these features may impact brain plasticity and cognitive abilities (Bangert and Schlaug, 2006; Hanna-Pladdy and MacKay, 2011). (2) Due to the cross-sectional design, caution is needed in drawing conclusions on the directionality of the here-observed associations. Although we accounted for a number of confounding variables, it may be possible that other unmeasured variables facilitate playing a musical instrument across the life course, such as genetic predispositions, personality traits or early-life environmental exposures (Corrigall et al., 2013; Zatorre, 2013; Altenmüller and Furuya, 2017). These factors could play a role in the observed relationships, warranting further investigation. (3) The assessment of musical activity was based on self-reports that were partially retrospective. The information was extracted from the LEQ, as a validated questionnaire that has been applied in the assessment of cognitive reserve/resilience (Chan et al., 2018; Collins et al., 2021). Self-reports can be biased by the current cognitive status of a person. However, our participants were cognitively unimpaired and screened for current and passed mental health conditions. Based on our study, it can be recommended that cohort studies include a more detailed and objective evaluation of lifetime musical activity (e.g., Okely et al., 2021) to strengthen validity and accuracy of the measure. (4) Finally, it is important to note that other aspects of musical activity, such as listening to music or choir singing, have beneficial effects in healthy and cognitively impaired OA, e.g., in the rehabilitation or intervention of neurological and neurodegenerative conditions (Särkämö, 2018; Gold et al., 2019).

CONCLUSION

To conclude, the present findings are promising to suggest that long-term participation in musical activity, as an accessible leisure-time activity, could be associated with greater brain and cognitive health in late life. Well-designed studies in OA are needed to further assess detailed information about the nature of playing a musical instrument and underlying functional and structural brain correlates associated with this complex multimodal activity.

DATA AVAILABILITY STATEMENT

The data that support findings of the present study are available on reasonable request from the DELCODE database. Requests to access these datasets should be directed to the German Center for Neurodegenerative Diseases (DZNE), Bonn.

ETHICS STATEMENT

The general study protocol for the DELCODE study was approved by the ethical committees of the medical faculties of all sites, i.e., the ethical committees of Berlin (Charité – Universitätsmedizin), Bonn (Medical Faculty, University of Bonn), Cologne (Medical Faculty, University of Cologne), Göttingen (Universitätsmedizin Göttingen), Magdeburg (Medical Faculty, Otto-von-Guericke University, Magdeburg), Munich (Medical Faculty, Ludwig-Maximilians-Universität), Rostock (Medical Faculty, University of Rostock), and Tübingen (Medical Faculty, University of Tübingen). The process was led and coordinated by the ethical committee of the medical faculty of the University of Bonn under the registration number: 171/13. The patients/participants provided written informed consent to participate in the DELCODE study.

AUTHOR CONTRIBUTIONS

AB, TK, AH, SR, MWa, GK, and MWi: conceptualization and design of the current study. OP, SF, JP, SA, ASc, IF, ASp, NR, SW, LK, JW, CB, FM, CM, LD, RY, KB, DJ, RP, B-SR, ST, IK, CL, MM, JH, PD, ME, KS, ED, FJ, SR, and MWa: overall design and implementation of the DELCODE study. AB, AZ, MG, and MW: methodology and statistical analysis. AB, AZ, TK, AH, SW, SR, MWa, GK, and MWi: interpretation of data. AB, AZ, TK, MG, AH, OP, SF, JP, SA, ASc, KF, IF, ASp, NR, SW, LK, JW, CB, FM, CM, LD, RY, KB, DJ, RP, B-SR, ST, IK, CL, MM, JH, PD, ME, KS, ED, FJ, SR, MWa, GK, and MWi: drafting and/or revision of manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.945709/full#supplementary-material

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Midlife occupational cognitive requirements protect cognitive function in old age by increasing cognitive reserve

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Introduction: Several lifestyle factors promote protection against Alzheimer's disease (AD) throughout a person's lifespan. Although such protective effects have been described for occupational cognitive requirements (OCR) in midlife, it is currently unknown whether they are conveyed by brain maintenance (BM), brain reserve (BR), or cognitive reserve (CR) or a combination of them.

Methods: We systematically derived hypotheses for these resilience concepts and tested them in the population-based AgeCoDe cohort and memory clinic-based AD high-risk DELCODE study. The OCR score (OCRS) was measured using job activities based on the O*NET occupational classification system. Four sets of analyses were conducted: (1) the interaction of OCR and APOE-ε4 with regard to cognitive decline (N = 2,369, AgeCoDe), (2) association with differentially shaped retrospective trajectories before the onset of dementia of the Alzheimer's type (DAT; N = 474, AgeCoDe), (3) cross-sectional interaction of the OCR and cerebrospinal fluid (CSF) AD biomarkers and brain structural measures regarding memory function (N = 873, DELCODE), and (4) cross-sectional and longitudinal association of OCR with CSF AD biomarkers and brain structural measures (N = 873, DELCODE).

Results: Regarding (1), higher OCRS was associated with a reduced association of APOE-ε4 with cognitive decline (mean follow-up = 6.03 years), consistent with CR and BR. Regarding (2), high OCRS was associated with a later onset but subsequently stronger cognitive decline in individuals converting to DAT, consistent with CR. Regarding (3), higher OCRS was associated with a weaker association of the CSF Aβ42/40 ratio and hippocampal volume with memory function, consistent with CR. Regarding (4), OCR was not associated with the levels or changes in CSF AD biomarkers (mean follow-up = 2.61 years). We found a cross-sectional, age-independent association of OCRS with some MRI markers, but no association with 1-year-change. OCR was not associated with the intracranial volume. These results are not completely consistent with those of BR or BM.

Discussion: Our results support the link between OCR and CR. Promoting and seeking complex and stimulating work conditions in midlife could therefore contribute to increased resistance to pathologies in old age and might complement prevention measures aimed at reducing pathology.

KEYWORDS

cognitive reserve, brain maintenance, brain reserve, mid-life cognitive demands, Alzheimer's disease, occupation

Introduction

The occurrence of dementia in old age is not inevitable. Even in the highest age groups, some individuals show only limited neurodegeneration (Braak et al., 2011), whereas others show only minor cognitive deficits in the presence of substantial neuropathological changes (Katzman et al., 1988; Azarpazhooh et al., 2020). This phenomenon has often been linked to concepts, such as cognitive reserve and its popular proxy measure of education (Stern, 2012; Stern et al., 2020). Higher education is associated with a reduced risk of dementia (Meng and D'Arcy, 2012) and has been shown to mitigate the effects of pathology on cognitive functions (Brayne et al., 2010; Wolf et al., 2019; Zahodne et al., 2019; Joannette et al., 2020; Soldan et al., 2020).

Importantly, cognitive activities beyond childhood and young adulthood, such as occupational cognitive activities in midlife (Kröger et al., 2008; Smart et al., 2014; Pool et al., 2016; Then et al., 2017), also provide protection against dementia (even when adjusting education). Midlife activities mediate parts of the protective association of education (Fujishiro et al., 2019), stressing the potential of continuing cognitive activities. Recently, Pool et al. (2016) proposed the "occupational cognitive requirements score" (OCRS) as a global indicator that still precisely reflects the fine-grained interindividual differences in cognitive activity levels associated with one's occupation. It is based on the Department of Labor's Occupational Information Network (O*NET) database (http://www.onetonline.org) that contains a detailed description of job characteristics and requirements. To derive the OCRS, only a job title (and a description of performed task where appropriate) is needed to map jobs to the O*NET database and score the occupational cognitive activities on a continuous scale. Pool et al. (2016) showed that the OCRS is related to slower cognitive decline in old age, but OCRS did not significantly interact with carrying an APOE-ε4 allele with respect to cognitive decline. Participants in this study were aged 65 years and above at baseline, were not selected based on cognitive status, and were followed up for 8 years on average.

The OCRS offers an another way to study the protective role of midlife occupational cognitive activities in cognitive decline and dementia based on occupational complexity (Kröger et al., 2008; Smart et al., 2014; Boots et al., 2015). While both occupational complexity and the OCRS measure to some degree the work-related cognitive demands, the OCRS assesses more directly the actual level of performed occupational cognitive activities.

Aims and research approach

In our study, we replicated the analysis of Pool et al. and extended it further, as explained in the following sections.

We aimed to extend previous research by exploring the specific resilience mechanisms that may convey the protective role of OCRS in cognitive decline. Research on reserve and resilience has developed definitions of three concepts that explain interindividual differences in the development of pathologies and their impact on cognitive function: cognitive reserve (CR), brain maintenance (BM), and brain reserve (BR). In this study, we refer to the definitions proposed by Stern et al. (2020), which are largely consistent with more recent definitions by the Collaboratory on Research Definitions for Reserve Resilience in Cognitive Aging Dementia (2022). However, we acknowledge that some differences in the definitions proposed by other authors may exist (Cabeza et al., 2018; Ewers, 2020). To assess the link between the OCRS and resilience concepts, we derived a set of hypotheses on expected associations of the OCRS with different outcomes in a population-based and memory clinic-based cohort. All hypotheses are graphically summarized in Figure 1. Of note, the hypotheses displayed in Figure 1 illustrate expected relationships in case the OCRS would solely act through the respective resilience concept. The empirical pattern of the results is then compared to these expectations.

We derived hypotheses for three different settings: (a) available direct measures of pathology and cognition in a memory clinic cohort; (b) no data on directly assessed pathologic markers but information on a genetic risk factor for pathology and cognitive decline in the general population; and (c) information only on cognitive trajectories in individuals developing dementia of the Alzheimer's type (DAT). For the latter case, we systematically derived the expected trajectories of the development of pathology and cognitive function for individuals with either high or low resilience in each

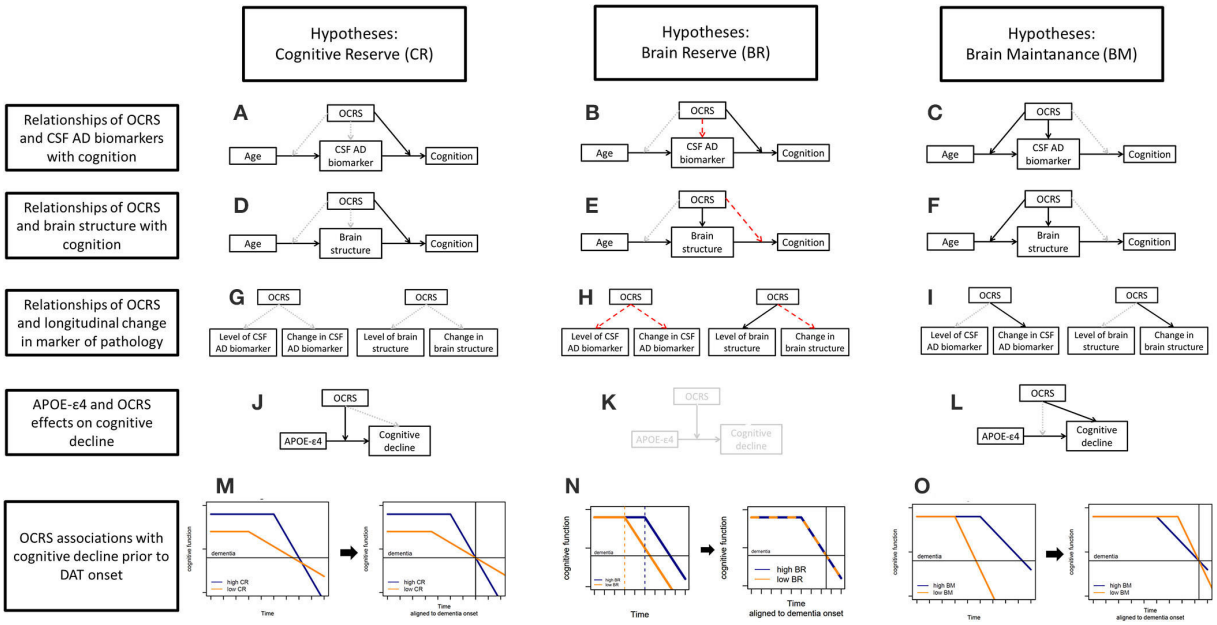

FIGURE 1
(A) Hypotheses for CR regarding the relationship of the OCRS and CSF AD biomarkers with cognition. **(B)** Hypotheses for BR regarding the relationship of the OCRS and CSF AD biomarkers with cognition. **(C)** Hypotheses for BM regarding the relationship of the OCRS w OCRS and CSF AD biomarkers with cognition. **(D)** Hypotheses for CR regarding the relationship of the OCRS and brain structure with cognition. **(E)** Hypotheses for BR regarding the relationship of the OCRS and brain structure with cognition. **(F)** Hypotheses for BM regarding the relationship of the OCRS and brain structure with cognition. **(G)** Hypotheses for CR regarding the relationship of the OCRS with longitudinal change in markers of pathology. **(H)** Hypotheses for BR regarding the relationship of the OCRS with longitudinal change in markers of pathology. **(I)** Hypotheses for BM regarding the relationship of the OCRS with longitudinal change in markers of pathology. **(J)** Hypotheses for CR regarding the relationship of the OCRS and APOE with cognitive decline in general population-based cohorts. **(K)** Hypotheses for BR regarding the relationship of the OCRS and APOE with cognitive decline in general population-based cohorts. **(L)** Hypotheses for BM regarding the relationship of the OCRS and APOE with cognitive decline in general population-based cohorts. **(M)** Hypotheses for CR regarding the relationship of the OCRS with cognitive decline prior to the onset of dementia of the Alzheimer's type (DAT). **(N)** Hypotheses for BR regarding the relationship of the OCRS with cognitive decline prior to the onset of dementia of the Alzheimer's type (DAT). **(O)** Hypotheses for BM regarding the relationship of the OCRS with cognitive decline prior to the onset of dementia of the Alzheimer's type (DAT). OCRS, occupational cognitive requirement score; APOE−+4, apolipoprotein E +4 allele; CSF, cerebrospinal fluid; CR, cognitive reserve; BM, brain maintenance; BR, brain reserve.

concept (Supplementary Figure 1). To specify hypotheses on the expected cognitive trajectories aligned to the onset of DAT, the derived prototypical cognitive trajectories were then moved graphically along the x-axis (time) until both trajectories aligned at a hypothetical dementia onset (Supplementary Figure 1, Figures 1M–O). We also discussed the caveats for interpretation in each setting with regard to the operational definitions proposed in the literature.

Hypotheses on the link of the OCRS with CR

Definition of CR

In our study, we defined CR as the brain's ability to actively adapt to the presence of pathologies and mitigate their impact on cognition, leading to higher cognitive functioning than expected based on pathologic brain changes (Stern et al., 2020). Historically, it has been assumed that the adaption of cognitive processes can compensate pathologies up to a "point of inflection" after which individuals with high reserve should show an accelerated decline in cognitive functioning (Stern, 2012). We consider this phenomenon to be a characteristic of CR. Furthermore, CR has been operationally defined as an amelioration of the effect of pathology on cognition; accordingly, a high level of a CR marker should relate to a weaker association between a measure of brain pathology and neuropsychological test performance (Stern et al., 2020).

Hypotheses and empirical tests of CR using direct assessments of pathology

First, we used data from the memory clinic-based German Center for Neurodegenerative Diseases (DZNE) Longitudinal Cognitive Impairment and Dementia Study (DELCODE) (Jessen et al., 2018), providing direct assessments of pathology and cognitive function in a population at increased risk for Alzheimer's disease (AD). We focused on two groups of pathology markers: (1) cerebrospinal fluid (CSF) biomarkers indexing AD pathologic changes (i.e., CSF Abeta42/40 and pTau181) since DELCODE is enriched for individuals at risk for AD (see Methods), and (2) measures of brain structure integrity

such as hippocampal volume and temporal cortex thickness obtained from MRI scans, as those brain regions are especially vulnerable to AD and age-related pathologic changes (Fjell et al., 2013), and global measures of brain structure and neuronal loss (i.e., total gray matter volume and CSF total tau). Regarding cognition, we focused on memory function, which is the most severely affected cognitive domain in AD, linked to AD and other neuropathologies (Wilson et al., 2019a), and is closely related to the integrity of the hippocampus and temporal lobe structures (Deweer et al., 1995). In addition, we assessed global cognitive functioning to examine the consistency of the findings when including data from other cognitive domains. Therefore, this cohort provided data to perform a recommended test for CR (Stern et al., 2020). If the OCRS mainly acts through CR, higher OCRS should be associated with a reduced association (i.e., a statistical interaction effect) of markers of AD pathology (Figure 1A), as well as markers of brain integrity with cognitive performance (Figure 1D).

Hypotheses and empirical tests of CR using genetic markers

Second, we aimed to assess the association between OCRS and cognitive decline in a population-based cohort of elderly individuals without dementia at baseline. This population-based cohort may allow for better generalizability of the results on OCRS, although a direct assessment of pathology is lacking. However, APOE-ε4, a strong genetic risk factor for AD (Genin et al., 2011), can serve as a proxy for a higher risk of pathologic development. Using such a risk factor for pathology is less precise than using a direct measure and can thus only provide putative evidence for a link between OCR and CR. Considering this limitation, it can be predicted that if the OCRS mainly acts through CR, higher OCRS should be associated with a reduced association of APOE-ε4 with cognitive decline, since the impact on pathologic changes should be mitigated in individuals with high CR. Statistically, this would be represented by a statistical interaction between APOE-ε4 and OCRS regarding cognitive decline (Figure 1J).

Hypotheses and empirical tests of CR using cognitive trajectories aligned to dementia onset

Third, we aimed to derive hypotheses on the link between OCR and CR in longitudinal cohorts without a direct assessment of pathologies or genetic risk markers as proxies. Notably, this can provide only low-level evidence for a link to CR compared to the empirical tests, including directly measured pathology. In this setting, we propose that the trajectory of cognition before and after the onset of dementia in individuals developing DAT should be examined. Importantly, all individuals who progressed to DAT developed some pathology. Therefore, assessing the trajectory of cognition in these individuals allows for the study of the adaptation of the brain to the progressive development of pathology. For individuals with a high CR, the predicted cognitive trajectories with progressively developing pathologies have been well-described (Stern, 2012). Herein, high CR should generally relate to an initially higher cognitive level and a later onset of cognitive decline (from individual-specific, previously stable levels), but a stronger cognitive deterioration afterward (Figure 1M, left plot). A stronger decline after symptom onset is expected due to the larger amount of pathology accumulated before the onset of pathology. When aligning these trajectories graphically to the onset of dementia (Figure 1M, right plot), a later onset, afterward, a stronger cognitive decline is expected for individuals with high CR. Interestingly, such a trajectory has already been demonstrated for individuals with higher education, a well-known proxy for CR (Amieva et al., 2014).

We additionally assessed whether there was evidence for a link between the OCRS and two other resilience concepts, BR and BM. In the following paragraphs, we provide definitions and empirical tests of the link between these concepts and how they relate to tests of the link to CR.

Hypotheses on the link of the OCRS with BR

Definition of BR

In line with previous definitions (Stern et al., 2020), we conceptualized BR as the fixed neurobiological capital at a given time point that might have been built up during development and is passively reduced in old age with increasing pathology. Herein, BR is the quantity of neurobiological capital available at that point in time and does not include any processes related to interindividual differences in changes in brain integrity (i.e., BM, see Section Hypotheses on the link of the OCRS with BM). More available resources (i.e., higher BR) can increase the threshold for pathology that does not affect cognitive function and, therefore, delay the onset of impairments (Stern et al., 2020).

BR requires a link between certain brain features (as an indication of neurobiological capital) and cognitive function. Intracranial volume has historically been used as a proxy for BR (Stern et al., 2020) because it relates to the fact that premorbid neurobiological capital is not affected by pathologic changes. Since high BR may increase the threshold to passively tolerate pathology, it operationally relates to individual differences in cognitive function and the risk of decline at a given level of pathology (Stern et al., 2020).

Hypotheses and empirical tests of BR using direct assessments of pathology

First, in the memory clinic-based sample, we assessed the association of the OCRS with markers of brain structure that

are related to cognitive function (i.e., hippocampal volume, temporal cortex thickness, and total gray matter volume). If OCRS acts through BR, there should be a cross-sectional association with these markers (Figure 1E). In contrast, if the OCRS mainly acts through BR, it should not relate to any longitudinal changes in brain markers in old age, as those changes are attributed to a different resilience concept [i.e., BM, see Section Hypotheses on the link of the OCRS with BM (Stern et al., 2020)]. We, therefore, examined the association of OCRS with changes in brain markers over a 1-year follow-up. If OCRS acts through BR, there should be no association with longitudinal changes in the markers of brain structure or pathology (Figure 1H). In addition, we tested the expected positive association of OCRS with intracranial volume, a proxy marker of BR that is not affected by pathology-related brain changes. Furthermore, if OCRS acts through BR, it should not be associated with cross-sectional levels or longitudinal changes in AD biomarkers since BR would not predict a direct effect on the development of neurodegenerative pathologies (Figures 1B,H; Stern et al., 2020). Notably, the link between OCRS and markers of neurodegenerative pathology and brain integrity is not part of the CR concept (Figure 1G) bearing the possibility that CR and BR may act at the same time. Therefore, the hypotheses described above focus on an additional aspect regarding the possible mechanism underlying the association of OCRS with reduced risk of cognitive decline.

Similar to CR, BR can influence the association between pathologic changes and cognition (Stern et al., 2020). However, the suspected mechanism may differ from that of CR. A high BR would result from high neurobiological resources that may passively buffer the impact of pathology on cognition until the depletion threshold of these resources. In contrast, CR is perceived as an active adaptation of cognitive processes to pathology, leading to the maintenance of high cognitive function. Both the proposed mechanisms can result in a reduced effect of pathologic alterations of proteins in the brain on cognition in cross-sectional data. Thus, if the OCRS acts through BR, a higher OCRS should be associated with a reduced association of AD biomarkers with cognition due to the buffering effect of higher neurobiological resources (Figure 1B). Operationally, this would manifest as a link of the OCRS with a measure of neurobiological resources and a reduced association of AD biomarkers with cognition that is attributable to these neurobiological resources. In contrast, BR would not be expected to modify the association between measures of brain integrity and cognition. This is because BR's protective effects should be derived from the brain structure itself and, consequently, once the structure is lost, its protective effect should be lost as well (Figure 1E). Importantly, a reduced association between markers of brain structural integrity and cognition is expected in individuals with high CR (Figure 1D). Thus, the differential predictions of BR and CR concepts regarding the reduction in the effect of brain integrity on cognitive function could provide suggestive evidence for a distinction between the two concepts. However, we emphasize that the results of these indirect tests cannot provide definite evidence. To this end, further confirmation by more direct assessments of neural mechanisms is needed (e.g., based on functional MRI). This could determine whether an active adaptation of cognitive processes or a passively increased threshold to tolerate pathology underlies this protective association. However, these assessments were not available in this study.

Hypotheses and empirical tests of BR using genetic markers

When examining the association of OCRS with cognitive decline in the general population depending on APOE-ε4, it is not possible to derive an empirical test of a link to BR due to the lack of a direct measure of neurobiological resources. The only possibility would be to examine the association of APOE-ε4 with cognitive decline. If the OCRS is linked to BR, one could speculate that higher OCRS could be associated with a reduced association of APOE-ε4 with cognitive decline due to a better passive tolerance of pathology due to higher neurobiological capital (Figure 1K). However, in the absence of a direct measure of neurobiological resources, any result cannot be unambiguously interpreted. For instance, CR and BR concepts would make identical predictions about the association of APOE-ε4 with cognitive decline, despite different underlying mechanisms.

Hypotheses and empirical tests of BR using cognitive trajectories aligned to dementia onset

In contrast, when studying the cognitive trajectories aligned with dementia onset in individuals developing an incident DAT, predictions derived from CR and BR concepts differ. During aging, high BR should relate to a later onset of dementia due to initially higher neurobiological resources. Rates of cognitive decline after the onset of deterioration from previously stable levels of cognition should develop at equal rates because BR acts through the passive increase of a threshold to tolerate pathology without any modification of the accumulation of or adaption to pathology (Figure 1N, left plot). Thus, when aligning those trajectories for dementia onset (Figure 1N, right plot), one would expect a complete alignment of cognitive trajectories and therefore no differences depending on BR. We acknowledge that the analysis only provides an indirect test of resilience mechanisms. Thus, it can only hint at the most likely underlying concept.

Hypotheses on the link of the OCRS with BM

Definition of BM

BM is defined as a characteristic of the brain that accumulates fewer age-related pathologies over time and maintains high levels of functional and structural integrity in old age that accounts for cognitive performance within aging and disease (Stern et al., 2020). Therefore, BM involves a link between longitudinal changes in markers of pathology and brain integrity and cognitive function and decline. A factor related to interindividual differences in BM should be related to a reduced change in pathology and brain structure over time.

Hypotheses and empirical tests of BM using direct assessments of pathology

In our memory clinic sample, we investigated changes in the markers of AD pathologic changes and brain integrity during follow-up. If the OCRS mainly acts through the BM, then the high OCRS should be associated with a lower rate of change in all examined markers because a higher BM should result in a reduced accumulation rate of pathologies (Figure 1I).

In addition, it can be hypothesized that if the OCRS mainly acts through BM, then higher OCRS should relate to lower levels of pathology at baseline, since a lower rate of accumulation should have already affected the development of pathologic markers prior to the baseline assessment in our memory clinic sample. Thus, longitudinal changes in pathology before study entry should be reflected in cross-sectional measurements. Since the BR concept also assumes higher levels of neurological capital and more preserved brain integrity, cross-sectional markers of brain structure *per se* cannot differentiate between the concepts. However, some suggestive indications for the differentiation between BM and BR can be derived using this type of data. Notably, cross-sectional differences in markers of AD pathologic change are not in line with BR but, in contrast, are predicted by BM (Figures 1B,C). In addition, if reduced age-related pathology due to BM is the underlying cause of cross-sectional differences in brain structure (and AD pathologic markers), then it can be expected that the association of age with these markers should be weaker in individuals with higher OCRS (Figures 1C,F; Steffener et al., 2014). This can be hypothesized because high BM is related to a reduced age-related accumulation of pathologies, and therefore, at higher levels of the BM, age should show a less pronounced association with pathology. However, the presence of a weaker association between age and pathologic markers in individuals with high OCRS does not imply that those must necessarily derive from BM since comparisons of individuals at different ages are not identical to the assessment of actual longitudinal changes. Cross-sectional comparisons can be affected by survival bias, since older age groups cannot include individuals who died at a younger age before the assessment. Therefore, these tests can only provide indications suggestive of BM. Nevertheless, in our study, we conducted these tests to make use of larger sample sizes of cross-sectional data.

Hypotheses and empirical tests of BM using genetic markers

With regard to data from general population-based cohorts with information on genetic markers only, it is not possible to directly assess the link between OCRS and BM due to the lack of a direct assessment of the pathology. However, in BM concepts, it is assumed that interindividual differences in the accumulation of pathology result in differences in the development of cognition. Therefore, in a general population based study, a higher OCRS should be associated with less cognitive decline if OCRS acts through BM (Figure 1J). Reduced cognitive decline in the general population-based study could derive from a later onset of pathology or a generally lower rate of accumulation. It is important to note that the presence of this association cannot demonstrate that OCRS is specifically related to BM, since lower rates of cognitive decline can have causes besides BM, including BR and CR. However, the absence of clear evidence for this association would argue against a link between the OCRS and BM because, in this case, the association would be expected.

Hypotheses and empirical tests of BM using cognitive trajectories aligned to dementia onset

When examining the trajectories of cognition aligned with dementia onset, it is again not possible to derive a direct test of a link between the OCRS and BM. However, the expected shape of the trajectory when the OCRS acts through BM differs from the respective expectations derived from CR and BR. A high BM should be related to a later onset of cognitive decline from previously stable levels of cognitive performance due to later onset and/or lower rate of the development of age-related pathologies. When focusing on individuals who develop dementia despite high BM, it is expected that those individuals will still show a slower rate of accumulation of age-related pathologies, leading to a longer-lasting and more gradual development of cognitive deterioration prior to dementia as compared to individuals with low BM (Figure 1O, left plot). Therefore, when aligning expected trajectories to dementia onset (Figure 1O, right plot), high BM should relate to an earlier onset (i.e., larger temporal distance between decline onset and dementia conversion due to more gradual accumulation of pathology prior to dementia) with a slower deterioration afterward. If BM manifests solely by a delayed onset of the accumulation of pathology but thereafter similar rates, then the OCRS should not relate to any interindividual differences in cognitive trajectories aligned to dementia onset if it acts mainly

through BM. In this case, predictions do not differ from those derived for BR (see Section Hypotheses and empirical tests of BR using cognitive trajectories aligned to dementia onset).

Methods

To test the full set of hypotheses, we used data from two multicenter German cohorts: the German Study on Aging, Cognition, and Dementia in Primary Care Patients (AgeCoDe) and the DELCODE cohort.

Sample description

AgeCoDe

We used data from 2,462 participants from the longitudinal, multicenter, prospective AgeCoDe study (Luck et al., 2007; Jessen et al., 2010). The study included randomly selected patients from 138 general practitioner (GP) practices in six German cities who were free of dementia and aged over 75 years at baseline. Exclusion criteria were consultations only by home visits, residence in a nursing home, severe illness the GP would deem fatal within 3 months, insufficient German language capabilities, deafness or blindness, inability to consent, and not being a regular patient of the participating practice. Among the 6,619 participants who could be successfully contacted, 3,327 provided informed consent and were included in the AgeCoDe cohort. The baseline examination took place between 2003 and 2004, with follow-up examinations every 18 months until 2015 (FU1–FU6) and three additional follow-ups every 10 months (FU7–FU9) in the so-called study on needs, health service use, costs, and health-related quality of life in a large sample of oldest-old primary care patients (85+) (AgeQualiDe). Questionnaires and neuropsychological assessments, including the Mini-Mental-State-Examination (MMSE) (Folstein et al., 1983), were administered at each visit. Dementia diagnoses were determined based on the respective assessments in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist at each visit. Dementia diagnosis was established according to the DSM-IV criteria based on the SIDAM interview (Zaudig et al., 1991). The interview assesses cognition (55-item cognitive test battery) and impairments in activities of daily living (14-item SIDAM-ADL) and includes the Hachinski–Rosen Scale (Rosen et al., 1980). Dementia diagnosis was based on the Global Deterioration Scale ($\geq$4) (Reisberg et al., 1982), if participants could not be personally interviewed. If sufficient information was provided, a clinical diagnosis of DAT was established according to the NINCDS-ADRDA criteria (McKhann et al., 1984). For the current analysis on cognitive trajectories prior to DAT onset, DAT participants without cerebrovascular events and those with events without temporal relationship to cognitive decline (i.e., mixed dementia) were considered. In AgeCoDe, occupational information (occupational title of the first job, last job, and longest-held job) was assessed at the second follow-up assessment. Based on this information, the OCRS was computed for 2,462 participants. Among those, 2,387 participants had information on the APOE genotype available or progressed to DAT during follow-up and could therefore be included in the current analysis (Figure 2).

All participants provided written informed consent prior to inclusion in the study. The study was approved by the ethics committee of all participating sites and conducted in accordance with the guidelines of the Declaration of Helsinki.

DELCODE

DELCODE (Jessen et al., 2018) is an observational, longitudinal, multicenter study conducted at 10 university-based memory clinics. The inclusion criteria were age $\geq$ 60 years, fluent German language skills, capacity to provide informed consent, and the presence of a study partner. Exclusion criteria were conditions clearly interfering with participation in the study or the study procedures, including significant sensory impairment, presence of specific medical conditions, or intake of specific psychoactive or anti-dementia drugs, as listed in Supplementary Text 1. DELCODE recruited patients with subjective cognitive decline (SCD), amnestic mild cognitive impairment (MCI), or DAT, who were referred to participating memory clinics. SCD patients had to report subjectively perceived cognitive decline causing concerns to the physician of the memory center and absence of a cognitive impairment defined as performance below -1.5 standard deviations (SD) in age, sex, and education-adjusted norms of the CERAD neuropsychological battery (Thalmann et al., 2000). MCI patients had to show at least a cognitive performance below -1.5 SD on the CERAD word-list delayed recall task. Patients with DAT had to show an MMSE score $\geq$18 and fulfilled the clinical NINCDS-ADRDA criteria (McKhann et al., 1984). In addition, a cognitively normal control group and cognitively normal first-degree relatives of patients with DAT were recruited *via* newspaper advertisements. SCD with concerns was used as an additional exclusion criterion for the control group. Detailed clinical and neuropsychological assessments and questionnaires, including an assessment of occupational information, were administered at baseline. In addition, MRI of the brain was performed, and CSF samples were collected from a subset of the participants (Figure 2). The participants were followed longitudinally during annual follow-up visits.

All participants provided written informed consent prior to inclusion in the study. The study was approved by the ethics committee of all participating sites and conducted in accordance with the guidelines of the Declaration of Helsinki.

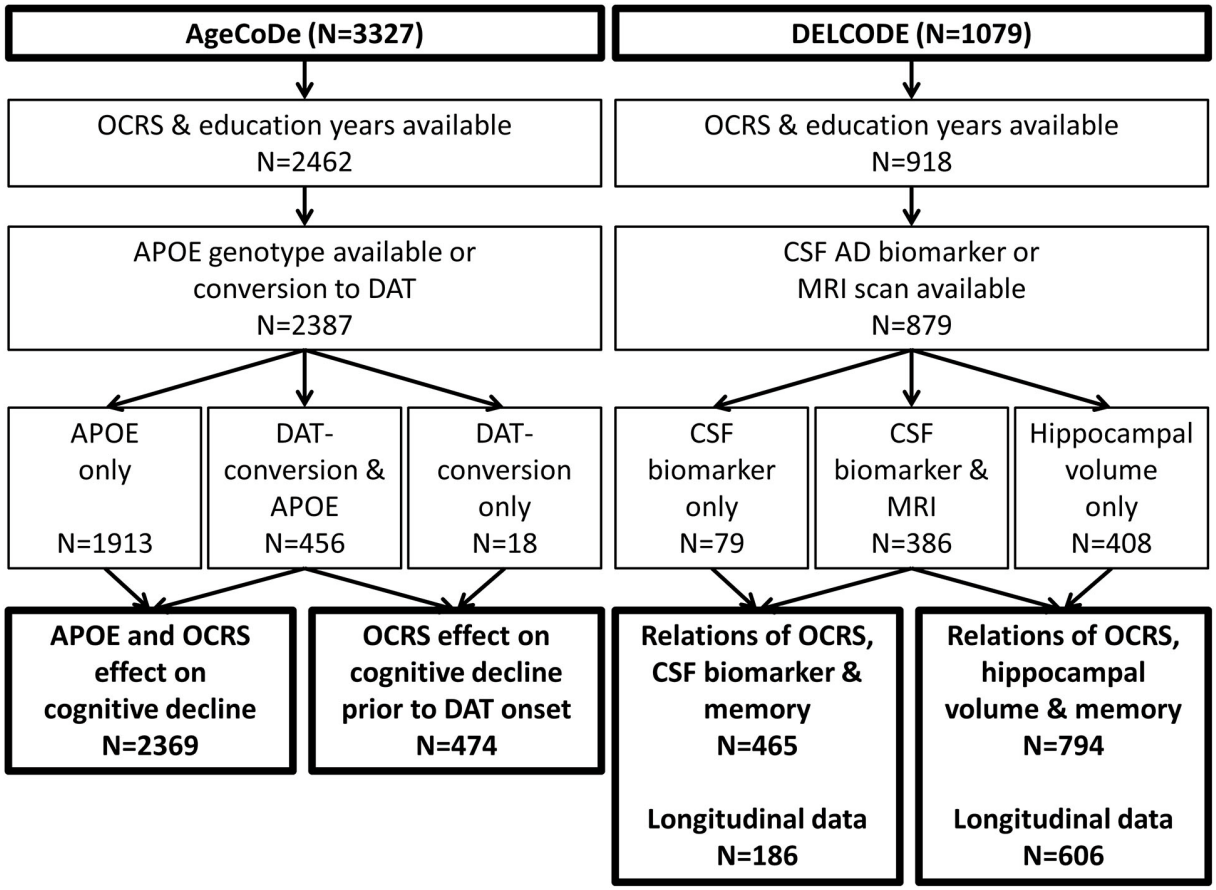

FIGURE 2
Flowchart of sample selection. APOE, apolipoprotein E; CSF, cerebrospinal fluid; DAT, dementia of the Alzheimer's type; OCRS, occupational cognitive requirement score.

Assessment of the OCRS

To assess the OCRS in AgeCoDe and DELCODE, information on the job title of the participant's longest-held occupation was assessed, together with major activities and duties. Based on this information, each occupation was coded according to the O*NET standard occupational classification (http://www.onetonline.org) by two independent raters. O*NET is the official occupational classification system of the U.S. Department of Labor, which codes occupations in a hierarchical structure and includes additional information on the skills and abilities required for the execution of each occupation.

AgeCoDe O*NET codes were derived as previously described (Forstmeier et al., 2012). In brief, two independent raters coded each AgeCoDe participant's longest-held occupation. Disagreements in coding were discussed with a third rater to reach consensus. The initial interrater agreement between the O*NET codes at the level of major groups (e.g., Life, Physical, and Social Science Occupations) was 86%. On the level of minor groups (e.g., Life Scientists and Physical Scientists), it was 74%. For specific occupations (e.g., Epidemiologist, Physicists, Chemists), the agreement was 66%.

In DELCODE, participants reported the main occupation (job title and main tasks) held in 5-year bands between the ages of 30 and 65 years, resulting in up to seven data points of occupation information per participant. Occupations were coded by four raters in total, with two raters independently coding half of the occupations of the first 394 participants and two raters coding half of the occupations of the remaining 683 participants. All ratings perceived as uncertain by any rater were discussed and reviewed at a consensus conference. To determine the interrater agreement, a random sample of 34 participants (238 occupational information data points) for the first 394 was drawn and coded by both raters. In addition, a random sample of 109 participants (677 occupational information data points) for the remaining 683 participants was drawn and coded by both raters. Initial agreement before the discussion of uncertain ratings was as follows: At the level of major groups in the O*NET

system, the interrater agreement was 80% for the first 394 and 73% for the remaining 683 participants. At the level of minor groups, the agreement was 69 and 57%, respectively. At the level of specific occupations, it was 57 and 40%, respectively. The occupation most often listed across the 5-year bands was considered the longest-held occupation. If occupations were listed equally often, the maximum resulting OCRS associated with those occupations was used.

In both cohorts, housewives were coded as "personal and home care aides," in line with previous research (Forstmeier et al., 2012). To build the OCRS in all cohorts, the level of cognition-related job activities of the longest-held occupation coded in O*NET (Supplementary Text 2) was summed in both cohorts, in line with the procedures described by Pool et al. (2016).

Assessment covariates

In both cohorts, education was assessed as years of formal education. In AgeCoDe, APOE-ε4 was coded as either present (i.e., at least one APOE-ε4 allele) or absent.

Assessment of cognitive outcomes

In AgeCoDe, global cognitive function was assessed using the MMSE (Folstein et al., 1983) at all assessments. In DELCODE, memory function was assessed using the memory factor score described by Wolfsgruber et al. (2020), which summarizes performance in the ADAS-Cog episodic memory tasks (Mohs et al., 1997), Free Cued and Selective Reminding Tests (Grober et al., 2009), Wechsler Memory Scale Logical Memory (Petermann and Lepach, 2012), CERAD figure recall (Thalmann et al., 2000), face–name association test (Polcher et al., 2017), and incidental learning of symbol number associations from the Symbol Digit Modality Test (Smith, 1982). As described in the introduction, memory was used as the primary outcome because of its strong link to AD and other neuropathologies (Wilson et al., 2019a). To assess the consistency of CR-related associations across cognitive domains, a global cognitive score (Wolfsgruber et al., 2020) was constructed as the average across factor scores of five cognitive domains (memory, executive function, working memory, visuospatial abilities, and language) and was used in a sensitivity analysis.

Assessment of MRI markers in DELCODE

In DELCDOE, MRI markers were derived from images obtained at nine scanner sites (3T) according to procedures described previously (Jessen et al., 2018). Volumetric data were obtained automatically using FreeSurfer version 7 (cross-sectional pipeline) based on whole-brain T1-weighted (1 mm isotropic) and partial-volume T2-weighted images optimized for the medial temporal lobe (0.5 × 0.5 × 1.5 mm). A standard "recon-all-all" default pipeline was applied including intensity normalization, surface registration to Talairach space, skull stripping, and subcortical segmentation. Next, computation of the statistics of the segmented subcortical structures (Fischl et al., 2002), white matter segmentation, tessellation, and inflation of pial and white matter surfaces, followed by cortical parcellation and generation of the statistics of the parcellated cortical regions, were performed (Fischl et al., 2004). In addition, we performed automatic hippocampal subfield segmentation using high-resolution T2-weighted images to obtain the hippocampal volumes (Iglesias et al., 2015). These procedures were applied separately to MRI scans obtained at baseline and at the first follow-up. For the current analyses, the volumes of the left and right hippocampus were averaged. Temporal cortex thickness was obtained by averaging the thickness of all segmented regions belonging to the temporal cortex (bilateral).

Assessment of CSF markers in DELCODE

CSF samples were collected by trained study assistants and processed, stored, and shipped to the central biorepository according to DZNE standardized operating procedures as previously described (Jessen et al., 2018). In brief, samples were aliquoted after collection, stored at −80°C in the DZNE biobank, and thawed once for ELISA measurement. Samples were assayed in technical duplicates, from which the mean and coefficient of variance (CV, percent of standard deviation divided by mean) of the duplicates were calculated. Samples with CV larger than 20% were repeated in measurement. On each ELISA plate, an eight-point calibrator curve, 39 samples, and one pooled and aliquoted internal reference CSF sample were measured. As DELCODE continuously and longitudinally collects samples, data were acquired throughout multiple ELISA plates and batches. The internal reference was used to control for the inter-run performance of the assay. Aβ42 and Aβ40 were quantified using the V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E), total Tau (tTau) was measured using V-PLEX Human Total Tau Kit (K151LAE) (Mesoscale Diagnostics LLC, Rockville, USA), and phospho-tau-181 (pTau181) was assessed using and INNOTEST PHOSPHO-TAU(181P) (81581; Fujirebio Germany GmbH, <city>Hannover</city>, Germany) assay according to vendor specifications. We used the ratio of Aβ42 to Aβ40 (Aβ42/40 ratio) to index amyloid pathology and ptau181 to index tau pathology in our study.

Statistical analysis

All analyses were performed using R version 3.4.3. The significance threshold was set at $\alpha = 0.05$.

Analysis of the association of the OCRS with CSF and MRI markers and cognition in DELCODE

Herein, the interaction of OCRS and AD biomarkers with cross-sectional memory function was assessed. Robust regression analyses were used, as implemented in the R package robustbase (Koller and Stahel, 2017; Maechler et al., 2018). Robust regression analyses were used to reduce the impact of extreme biomarker values observed in the DELCODE data. We modeled the interaction of the OCRS and either Aβ42/40 ratio, pTau181 (i.e., markers of AD pathology), hippocampal volume or temporal cortex thickness, and CSF total tau or total gray matter volume (i.e., global markers of neuronal loss) on memory function in separate models. In sensitivity analyses, the global cognitive score was used as the outcome.

In addition, the association of OCRS with all the aforementioned markers was assessed. Furthermore, the interaction of the OCRS and age with regard to CSF and MRI markers was estimated. CSF markers were log-transformed prior to analysis to approximate normal distribution. The association of OCRS with the estimated intracranial volume was also examined.

Furthermore, we tested the association of OCRS with longitudinal changes in all CSF and MRI markers using linear mixed models. Herein, we included only individuals with more than one marker assessment (CSF: $N = 189$; MRI: $N = 606$). Solely one follow-up assessment after 1 year was available for MRI markers (follow-up range: 0.77–1.58 years). Annual CSF assessments were repeated once in 146 individuals, twice in 40 individuals, and thrice in three individuals (follow-up range: 0.96–5.05 years). The lme4 package (Bates et al., 2015) was used to analyze the changes in CSF and MRI markers. Models with random intercepts were fitted using maximum likelihood estimation to account for repeated observations taken from the same individuals. Random slopes were not included because of the limited number of repeated observations. In the first step, the main effect of OCRS across all longitudinal observations was tested by including OCRS as a predictor in the mixed model. In the second step, we tested whether OCRS was associated with changes in markers from the baseline by including an interaction between OCRS and time from baseline to the model. Significance was assessed using the likelihood ratio test.

All analyses were controlled for age, sex, years of education, whether participants were already retired and the interaction of the variables with time. Retirement was included as a covariate because previous research has shown that retirement can affect cognition (Celidoni et al., 2017) and could relate to certain job characteristics. In the case of analyses of the MRI markers, we also controlled for intracranial volume at baseline and at the scanner site. Continuous predictors were z-standardized based on the total sample to facilitate the interpretation and comparability of the estimates. Patients with DAT were excluded from the sensitivity analysis.

In an exploratory analysis, the link of the OCRS with change in cognition was assessed (Supplementary Text 3).

Analysis of cognitive decline in AgeCoDe

To replicate the analyses of Pool et al. we analyzed the association of OCRS with cognitive decline in AgeCoDe. We used single-class univariate latent process mixed models, as implemented in the R package lcmm (Proust-Lima et al., 2011, 2017). Latent process mixed models estimate a latent process that represents the true level and change in a cognitive outcome and relate this latent process to observed data using a parameterized link function. This link function accounts for unequal interval scaling of cognitive outcomes, a common methodological limitation that is not considered by traditional statistical methods (Proust-Lima et al., 2011). To model the MMSE in AgeCoDe, different parametrized link functions (linear, quadratic I-splines with knots placed either equidistant across the outcome range or at percentiles of the distribution and beta cumulative distribution link function) were compared based on the Bayesian information criterion (BIC). In addition, the fixed effects of linear and quadratic time from baseline and the respective random effects were included and compared based on the BIC.

To assess the association of OCRS with cognitive decline, OCRS and its interactions with polynomials of time from baseline were modeled as fixed effects. Analyses were controlled for fixed effects of age, sex, years of education, and presence of at least one APOE-ε4 allele, as well as their interactions with polynomials of time (e.g., time*age, time^2*age). To assess the interaction of OCRS with the APOE-ε4 allele, the three-way interaction of OCRS, APOE-ε4, and the respective polynomials of time were included in the fixed effects.

Analysis of cognitive decline prior to DAT onset in AgeCoDe

To assess whether the OCRS modulates cognitive change prior to dementia onset, generalized additive mixed models (Wood, 2004, 2011) (GAMM) were used as implemented in the R package mgcv (Wood, 2011). GAMM is a statistical method that allows the flexible consideration of non-linear associations between variables in longitudinal data. To this end, the link between a predictor and longitudinally measured outcome is modeled as a smooth function that can represent a very wide range of non-linear functional forms without

the need for a priori assumptions about the shape of the functional form. Smooth functions can be modeled using different statistical techniques, such as (e.g., cubic regression or thin-plate regression) splines (Wood, 2003). Since the trajectory of cognition aligned to dementia onset can be expected to follow a highly non-linear shape (Amieva et al., 2014), GAMM offers a useful approach to model these data.

In this study, a total of 474 participants developing DAT during the follow-up of AgeCoDe and with information on OCRS were included, and their cognitive decline was assessed using the MMSE. Since GAMM does not allow for the inclusion of the beta cumulative distribution link function to account for non-equal interval scaling, the normalized version of the MMSE was used (Philipps et al., 2014), which accounts for the methodological problem based on an established normalizing transformation. First, to exclude the influence of extreme follow-up times in a few individuals on the model results, observations made in only 5% of the participants (i.e., >12.38 years before DAT onset and >3.31 years after DAT onset) were excluded.

Time to dementia onset was modeled using cubic regression splines, and the random slope of time relative to DAT onset and a random intercept were modeled to account for repeated measurements taken from the same individuals. In the next step, we included age, years of education, and OCRS as covariates and modeled their main effects on cognition using cubic regression splines. In addition, a fixed effect for sex and a time-varying indicator indexing the first MMSE assessment were included. The indicator of the first MMSE assessment was used to account for the practice effects which affect all measurements of the MMSE except for the first assessment. This was necessary because the first assessment of the MMSE (performed at the baseline of the study) was performed with different temporal lags relative to dementia onset (because individuals showed dementia conversion at different time points during follow-up). For example, for an individual converting at follow-up one, the assessment prior to dementia onset would be unaffected by the practice effect. In contrast, for an individual converting at follow-up 2, the assessment prior to dementia onset would be affected by the practice effect. This individual-specific influence needs to be considered to describe the natural trajectories of cognition independent of practice effects.

To assess the association of covariates with changes in cognition, tensor product interactions (Wood, 2006) (based on cubic regression splines) were fitted between the time to dementia onset and each continuous covariate. In addition, a smooth-factor interaction between time and sex (since sex is a categorical covariate) was included.

All analyses were fitted using maximum likelihood. Analyses were repeated using thin-plate regression splines (Wood, 2003), using all available observations and increasing the number of basis dimensions.

Results

The descriptive statistics for the AgeCoDe and DELCODE participants in each analysis are presented in Table 1. Descriptive statistics for DELCODE stratified by diagnosis are provided in Supplementary Table 1.

Association of the OCRS with MRI and CSF biomarkers and cross-sectional cognition in DELCODE

First, we explored whether OCRS mainly acts through CR, BM, or BR. Herein, we turned to the DELCODE study, where direct measurements of pathology are available in participants across a broad spectrum of clinical impairments and AD risks. Interaction analyses using robust regression models (Supplementary Table 2) showed a reduced association of the CSF Aβ42/40 ratio (b = −0.11, SE = 0.04, p = 0.003, Figures 3A,B) with memory function in individuals with higher as compared to lower OCRS. No modification in the association of CSF pTau181 with memory function by OCRS was found. In contrast, high OCRS was associated with a reduced association of hippocampal volume (Est = −0.08, SE = 0.03, p = 0.001, Figures 3C,D) and temporal cortex thickness (Est = −0.09, SE = 0.03, p = 0.0007) with memory function. There was a trend-level interaction effect of OCRS and total gray matter volume (Est = −0.05, SE = 0.03, p = 0.061), but no interaction between OCRS and tTau. The results on Aβ42/40 ratio, hippocampal volume, and temporal cortex thickness were significant after Bonferroni correction for multiple testing. Repeating analyses with global cognition as the outcome (Supplementary Table 3) replicated results on memory function, but additionally showed an interaction between OCRS and total gray matter volume (Est = −0.05, SE = 0.02, p = 0.039). All analyses were adjusted for age, sex, and years of education. The results did not change substantially when patients with DAT were excluded, although the interaction effects of the OCRS with MRI markers were reduced and only significant at the trend level (Supplementary Tables 2, 3). Further excluding MCI patients from the sample resulted in no significant interaction effects in our sample, probably due to variance restriction and selection bias (Supplementary Table 4; see Section Moderating role of OCRS in the link between directly measured pathology and cross-sectional cognitive function for discussion).

Furthermore, we found that the OCRS itself was not related to the cross-sectional levels of Aβ42/40 ratio and pTau (Supplementary Table 5). There was a cross-sectional positive association of the OCRS with hippocampal volume (Est = 37.16, SE = 14.37, p = 0.009), temporal cortex thickness (Est = 0.01, SE = 0.01, p = 0.048), and total gray matter

TABLE 1 Descriptive statistics.

	AgeCoDe				DELCODE					
	APOE sample		DAT converter sample		Whole cohort		MRI sample		CSF sample	
	Mean/*N*	SD/%	Mean/*N*	SD/%	Mean/*N*	SD/%	Mean/*N*	SD/%	Mean/*N*	SD/%
Age at baseline (Mean/SD)	79.37	3.45	80.33	3.49	71.27	6.17	71.11	6.12	71.13	6.04
Female sex (*N*/%)	1,553	65.6%	351	74.1%	441	50.5%	406	51.1%	226	48.6%
Years of education (Mean/SD)	12.05	2.28	11.89	2.25	14.49	3.00	14.51	3.01	14.35	2.91
MMSE at baseline (Mean/SD)	27.61	1.91	27.06	2.06	28.45	2.35	28.53	2.30	28.22	2.45
OCRS (Mean/SD)	3.17	0.85	3.05	0.82	3.94	0.82	3.95	0.82	3.94	0.84
Retired (*N*/%)	–	–	–	–	736	84.3%	670	84.4%	388	83.4%
APOE-ε4 carrier (*N*/%)	503	21.2%	135	28.5%	303	35.0%	265	33.7%	174	37.6%
Biomarker of pathology at baseline										
Aβ42/40 (Mean/SD)	–	–	–	–	0.08	0.03	0.09	0.03	0.08	0.03
pTau181 (Mean/SD)	–	–	–	–	61.14	31.98	60.17	31.83	61.14	31.98
tTau (Mean/SD)	–	–	–	–	451.51	269.21	448.87	267.96	451.51	269.21
HCvol (Mean/SD)	–	–	–	–	2,972.85	413.09	2,972.85	413.09	2,954.68	443.30
Diagnostic groups										
Controls (*N*/%)	–	–	–	–	201	23.0%	195	24.6%	82	17.6%
SCD (*N*/%)	–	–	–	–	364	41.7%	327	41.2%	188	40.4%
aMCI (*N*/%)	–	–	–	–	150	17.2%	129	16.2%	97	20.8%
DAT (*N*/%)	–	–	–	–	84	9.6%	75	9.4%	53	11.4%
DAT relatives (*N*/%)	–	–	–	–	74	8.5%	68	8.6%	45	9.7%
Follow-up										
Observation time (in years)	6.03	4.35	8.06	3.52	2.81	1.72	1.04[a]	0.08[a]	2.61[b]	0.91[b]

[a]Follow-up time specifically for MRI measures; [b]follow-up time specifically for CSF measures. Aβ42/40, CSF Aβ42/Aβ42 ratio; aMCI, amnestic cognitive impairment; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DAT, dementia of the Alzheimer's type; HCvol, average of left and right hippocampal volumes; N, sample size; OCRS, occupational cognitive requirement score; pTau181, CSF phospho-tau-181; SCD, subjective cognitive decline; SD, standard deviation; tTau, CSF total Tau.

volume (Est = 5,731.9, SE = 1,490, $p = 0.0001$), but no association with tTau (Supplementary Table 5). However, the association of OCRS with MRI markers did not depend on age, as indicated by the absence of OCRS × age interactions (Supplementary Table 5).

In line with these cross-sectional results, longitudinal data analyses (CSF: $N = 189$, number of observations = 424; MRI: $N = 606$, number of observations = 1,212; Supplementary Table 6) showed an association between the OCRS and general levels of hippocampal volume (Est = 37.77, SE = 16.43, $p = 0.020$) and general levels of total gray matter volume (Est = 5,164.0, SE = 1,645.1, $p = 0.001$) across all longitudinal assessments. We found no association between Aβ42/40 ratio, pTau, temporal cortex thickness, or tTau (Supplementary Table 6). In addition, there was no association between OCRS and longitudinal change from baseline in any pathologic marker (Supplementary Table 6). The results were similar when individuals with DAT were excluded (Supplementary Table 6). When excluding MCI and DAT patients from the sample, only the cross-sectional association of the OCRS with total gray matter volume remained (Supplementary Tables 7, 8). Controlling for follow-up time did not change the results substantially (Supplementary Table 8).

OCRS did not predict the estimated intracranial volume (whole sample: Est = 9,026, SE = 7,063, $p = 0.202$; excluding DAT cases: Est = 13,661, SE = 7,453, $p = 0.067$).

Exploratory analyses of longitudinal cognitive change (Supplementary Text 3) revealed a just significant interaction of OCRS and temporal cortex thickness regarding cognitive decline in the analysis excluding patients with MCI and DAT [$Chi^2_{(2)} = 6.042$, $p = 0.049$; Supplementary Tables 9–11]. This association did not survive correction for multiple testing. No other significant associations with cognitive change were found.

Longitudinal cognitive decline in AgeCoDe

Next, we studied the association of the OCRS with cognitive decline in the MMSE in AgeCoDe to replicate the results of Pool et al. (2016). The lowest BIC suggested that latent process mixed models of MMSE trajectories were best represented by models including a random intercept and random slope of time and time squared, as well as a beta cumulative distribution link function to adjust for non-equal interval scaling (Proust-Lima et al., 2011).

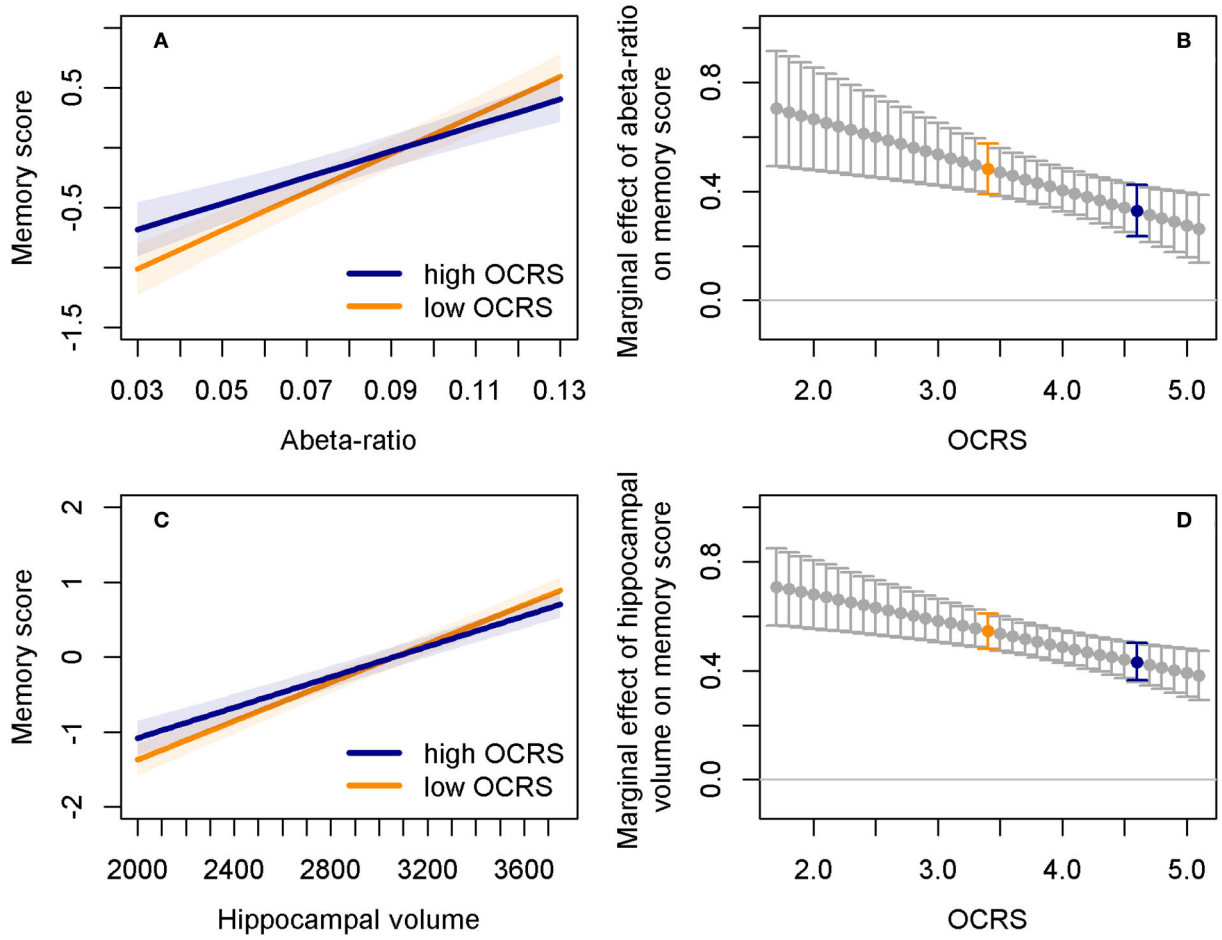

FIGURE 3
Interaction effects of OCRS with Aβ42/40 ratio and hippocampal volume regarding cross-sectional memory function. **(A)** Predicted memory factor scores depending on Aβ42/40 ratio in individuals with either low (25th percentile, orange line) or high (75th percentile, blue line) OCRS levels. Shaded areas indicate 95% confidence intervals. **(B)** Marginal effects of the Aβ42/40 ratio depending on OCRS levels. Bars indicate 95% confidence intervals. Marginal effects indicate the change in the memory factor when the Aβ42/40 ratio increases by one standard deviation. It is computed as the sum of the coefficients of the Aβ42/40 ratio and the Aβ42/40 ratio*OCRS interaction term. Blue dots and bars correspond to the predicted trajectory for individuals with high OCRS (blue line) in plot **(A)**. Orange dots and bars correspond to the predicted trajectory for individuals with low OCRS (orange line) in plot **(A)**. Marginal effects indicate that effects of Aβ42/40 ratio on memory function are stronger at lower levels of the OCRS. **(C)** Predicted memory factor scores depending on the averaged left and right hippocampal volume in individuals with either low (25th percentile, orange line) or high (75th percentile, blue line) OCRS levels. Shaded areas indicate 95% confidence intervals. **(D)** Marginal effects of the hippocampal volume depending on OCRS levels. Bars indicate 95% confidence intervals. Interpretation analogous to **(B)**, that is, marginal effects indicate that the effects of hippocampal volume on memory function are stronger at lower levels of the OCRS. Abeta ratio, cerebrospinal fluid Aβ42/Aβ42 ratio; OCRS, occupational cognitive requirement score.

Models adjusted for age, sex, educational level, and carrying the APOE-ε4 allele showed no association of OCRS with the speed of cognitive decline in all AgeCoDe participants with information on OCRS [$Chi^2_{(2)} = 0.314$, $p = 0.855$, Supplementary Table 12]. However, individuals with high OCRS and carrying the APOE-ε4 allele had a significantly weaker association with cognitive decline than individuals with low OCRS [$Chi^2_{(2)} = 6.931$, $p = 0.031$, Supplementary Table 12], as shown by predicted MMSE trajectories (Figure 4A). In addition, we observed a reduced difference between APOE-ε4 allele carriers and non-carriers in MMSE decline at high levels of OCRS (Figure 4B). Notably, higher OCRS was associated with higher baseline levels of cognition (Supplementary Table 12).

Longitudinal cognitive decline prior to DAT onset in AgeCoDe

Finally, MMSE trajectories aligned to dementia onset in AgeCoDe participants who progressed to DAT were

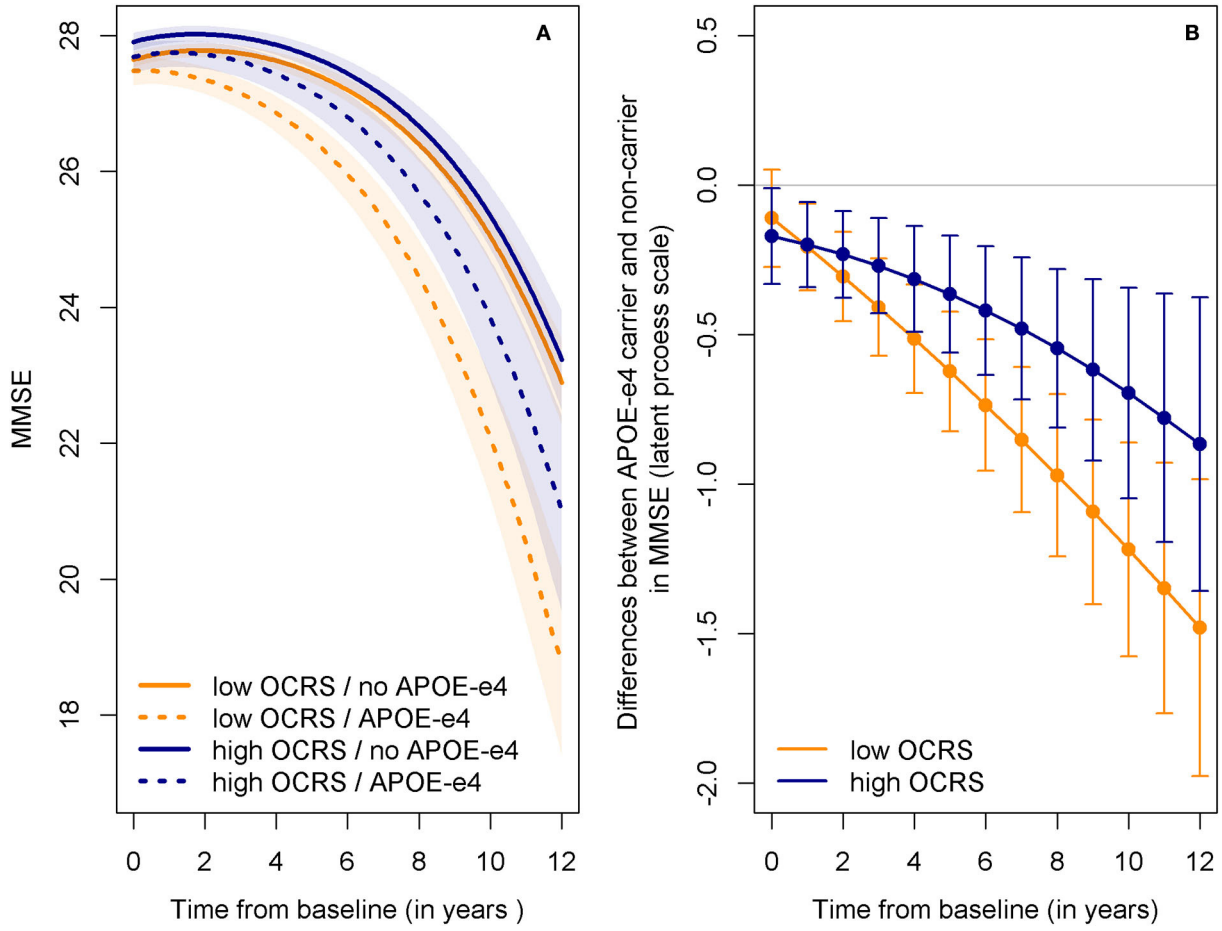

FIGURE 4
Predicted trajectories of cognitive decline in AgeCoDe depending on OCRS and APOE-ε4. **(A)** Predicted trajectories in MMSE for APOE-ε4 carrier and non-carrier with either low (25th percentile) or high (75th percentile) OCRS levels. Shaded areas indicate 95% confidence intervals. While APOE-ε4 is generally associated with a stronger cognitive decline (steeper slope for dotted compared to straight lines), this difference is larger in individuals with low OCRS (orange lines) compared to high OCRS (blue lines). **(B)** Differences in MMSE between APOE-ε carrier and non-carrier at different time points for individuals with either low (25th percentile) or high (75th percentile) OCRS levels. Bars indicate 95% confidence intervals. Differences are presented on the scale of the latent variable in the latent process mixed models (Proust-Lima et al., 2011), not on the scale of the observed variable (i.e., the MMSE). Differences are generally lower (i.e., closer to zero) for individuals with high (blue line) as compared to low (orange line) OCRS values. APOE-e4, apolipoprotein E ε4 allele; MMSE, Mini-Mental-State-Examination; OCRS, occupational cognitive requirement score.

modeled to complement previous empirical tests of conceptual predictions using the large prospective AgeCoDe study. The GAMM showed that the OCRS significantly modified the shape of the MMSE trajectory ($F = 3.26$, edf $= 6.61$, $p = 0.004$, Supplementary Table 13, Figure 5). Plots illustrating the non-linear association of the OCRS prior to DAT onset over the entire range of the variables are shown in Supplementary Figure 2. As can be seen from these figures, a high OCRS is associated with stable or even slightly increasing cognitive performance until ∼5 years before DAT diagnosis. During the same period, a low OCRS was already associated with a slight cognitive decline. Subsequently, high OCRS is associated with a stronger cognitive decline, whereas low OCRS is associated with a more gradual, lower cognitive decline.

Discussion

This study aimed to examine whether work-related cognitive activities in midlife, as captured with the OCRS (Pool et al., 2016), protect against cognitive decline in old age, and whether such a protective association would be based on CR, BR, or BM (see Figure 6 for a graphical summary of the results).

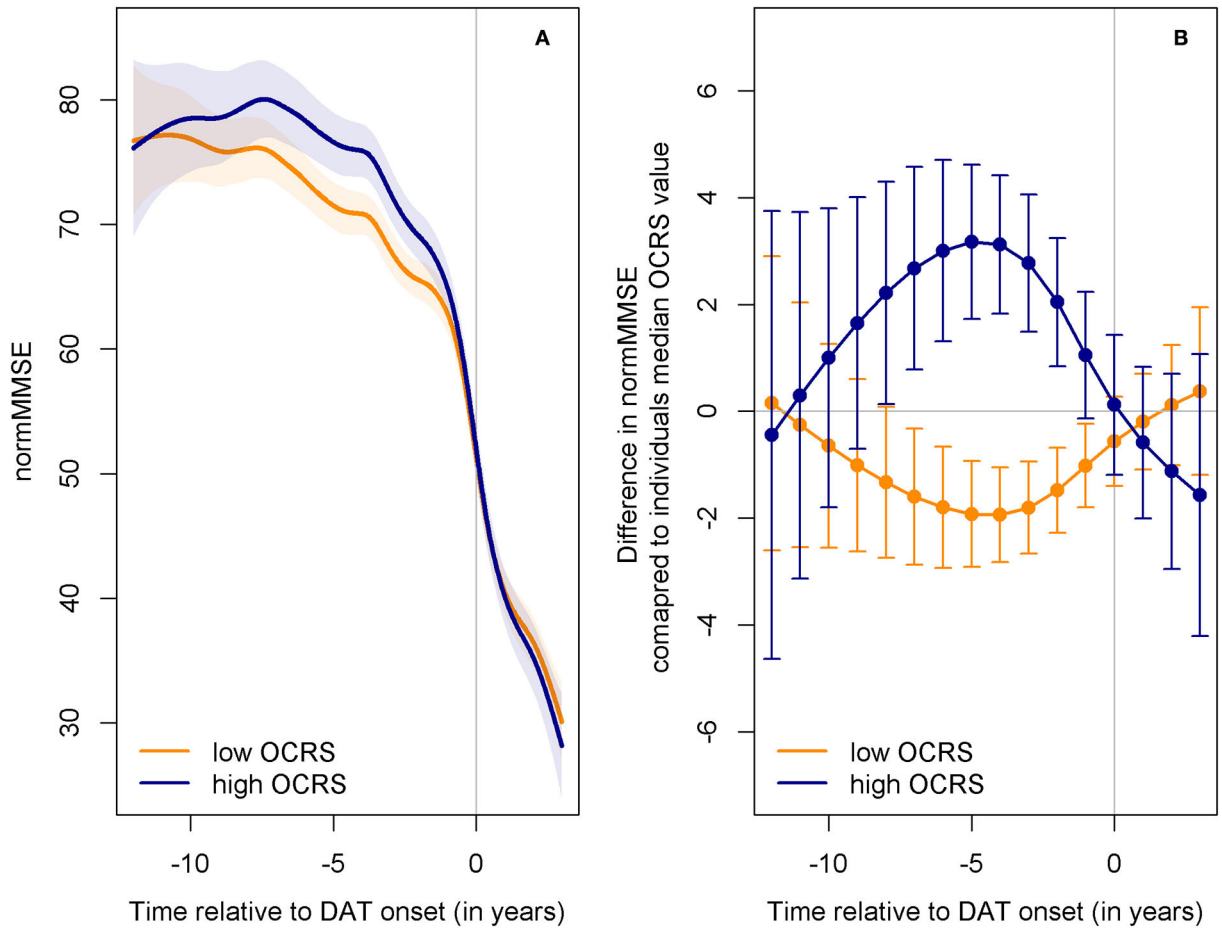

FIGURE 5
Predicted trajectories of cognitive decline in AgeCoDe before DAT onset depending on OCRS. **(A)** Predicted trajectories in the normalized MMSE (normMMSE) (Philipps et al., 2014) relative to the onset of DAT for individuals with either low (25th percentile) or high (75th percentile) OCRS levels. The normalized MMSE has a range of 0 to 100. Shaded areas indicate 95% confidence intervals. Individuals with high OCRS (blue line) show stable cognitive function for a longer period than individuals with low OCRS (orange line). However, they decline stronger after the onset of deterioration. Both groups show equal levels of performance at dementia onset. Afterward, high OCRS is associated with slightly lower levels of cognitive function. **(B)** Predicted differences of individuals with high (75th percentile) or low OCRS (25th percentile) compared to individuals with median OCRS values at different time points relative to DAT onset. Bars indicate 95% confidence intervals. Differences are computed from the sum of OCRS smooth terms [ti(OCRS) in the mgcv package] and OCRS and time tensor product interaction terms [ti(time,OCRS) in the mgcv package]. While high OCRS (blue line) shows an increasingly protective association with cognitive function until ∼5 years before dementia onset, this association diminishes and predicted cognition is even lower than in individuals with low OCRS (orange line) after DAT onset. DAT, dementia of the Alzheimer's type; normMMSE, normalized Mini-Mental-State-Examination; OCRS, occupational cognitive requirement score.

Moderating role of OCRS in the link between directly measured pathology and cross-sectional cognitive function

We found a reduced association of Aβ42/40 ratio with cross-sectional memory and global cognitive function in participants with higher OCRS in DELCODE, supporting a link between the OCRS and CR or BR, since a reduction in the impact of AD pathology on cognitive function is expected by these concepts. In contrast, the absence of any longitudinal association of the OCRS itself with any AD CSF level does not support a relationship with BM, as the rate of accumulation of pathology should be lower in individuals with high BM. The absence of cross-sectional differences (especially at older ages) does again not support a link of the OCRS to BM.

When focusing on measures of brain structure and neural loss, we again found support for a link between OCRS and CR mechanisms, as high OCRS was associated with a reduced cross-sectional association of hippocampal volumes and temporal cortex thickness with memory and global cognitive function. In contrast, the BR theory does not expect this reduced association

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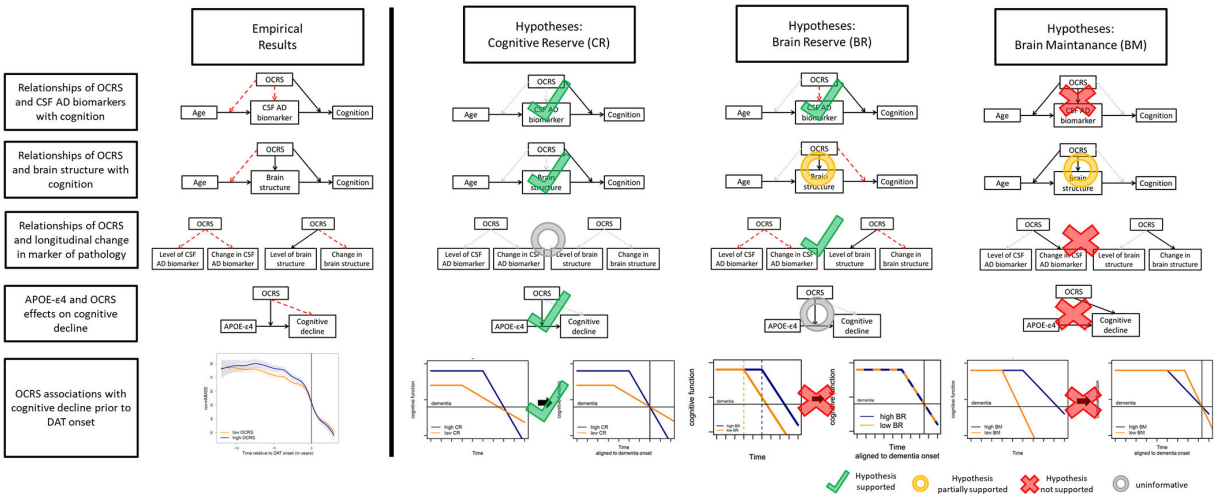

FIGURE 6
Graphical illustrations of hypothesis test results for CR, BM, and BR. In the graphical illustrations of hypotheses **(right side)**, black arrows linking boxes indicate expected association, red dashed arrows indicate associations inconsistent with the predictions by the respective resilience concept, and gray dotted arrows indicate no expectation regarding association by the respective resilience concept. Arrows pointing toward other arrows indicate an expected statistical interaction effect. In the bottom row, plots on the left illustrate the typical development of cognition over time. Bold arrows indicate the alignment of time to the onset of dementia (horizontal black line) that is a shift along the x-axis. In the graphical illustrations of empirical results **(left side)**, black arrows indicate supported associations while red arrows indicate non-significant associations not supported by our data. OCRS, occupational cognitive requirement score; APOE-ε4, apolipoprotein E ε4 allele; CSF, cerebrospinal fluid; CR, cognitive reserve; BM, brain maintenance; BR, brain reserve.

because the protective effects of BR should be derived from the brain structure itself and should therefore be lost (or at least substantially diminished) once the brain structure itself is reduced. In addition, there was no association between OCRS and intracranial volume, a common proxy for BR, which does not support the connection of OCRS to this concept. However, we observed a cross-sectional association of the OCRS with hippocampal volume, temporal cortex thickness, and total gray matter volume, as expected by BR and BM theory. This finding is consistent with previous research linking occupational activity with brain structure (Suo et al., 2012; Kaup et al., 2018; Habeck et al., 2019; Rodriguez et al., 2021a). Notably, but contrary to predictions based on BM theory (Nyberg et al., 2012; Steffener et al., 2014), the cross-sectional association of OCRS with brain structural measures was not stronger in older individuals and was not detectable with regard to longitudinal changes in MRI markers. However, the short follow-up in the currently available DELCODE data limited our ability to detect longitudinal changes in the markers of pathology, and survival bias may have affected the interaction between OCRS and age regarding the markers. Previous studies examining the link of other proposed proxy measures of CR with longitudinal change in markers of pathology have not found clear evidence for a consistent association as shown in a recent review by Soldan et al. (2020). Our results on the OCRS are consistent with these findings, but more research in larger studies with longer follow-up on pathologic markers is required for confirmation.

In summary, these analyses support the predictions made by CR theory, but only partially support the expectations derived from BR and BM theory.

Of note, interactions of the OCRS with markers of pathology regarding cross-sectional cognitive function supporting a link to CR were not present when excluding MCI patients. However, excluding MCI patients may have artificially attenuated the effect of CR on the interplay of cognition and pathology. Both MCI and SCD patients (the largest group in the remaining sample) were recruited for memory clinics and delineated based on their cognitive performance. Thus, at the same level of pathology, individuals with high CR are more likely to receive an SCD diagnosis (due to better compensation of pathology), while individuals with low CR are more likely to receive an MCI diagnosis (due to less compensation). Excluding individuals with MCI, therefore, depletes the sample from individuals with low CR or higher levels of pathology thereby counteracting the ability for detecting interaction effects consistent with CR in the DELCODE sample. In line with this, MCI patients descriptively showed lower levels of OCRS if they also showed higher levels of pathology as compared to SCD patients. Nevertheless, further research on cognitively normal individuals

recruited from the general population is needed to test whether a link of the OCRS with CR can be shown in cognitively normal individuals.

OCRS and cognitive decline in older individuals

We found that higher OCRS is not generally related to slower cognitive decline in individuals aged 75 years or above from the AgeCoDe cohort; instead, it is associated with a reduction in the association of carrying an APOE-ε4 allele with cognitive decline. Notably, it was previously shown in AgeCoDe that specific cognitive demands are especially important in mitigating the relationship between APOE-ε4 and cognitive decline (Rodriguez et al., 2021b). In the current study, we provide novel evidence that the OCRS is a reliable and easily implementable global measure for assessing work-related cognitive requirements that are associated with preserved cognitive function in individuals at a genetically elevated risk for pathology. As shown in our study, the information provided by the OCRS extends beyond the information included in the educational level and should therefore complement assessments of protective cognitive activities. Our results differ from those of Pool et al. (2016), who found a general protective association with cognitive decline across all participants, but no significant interaction of the OCRS with APOE-ε4 ($p = 0.11$). Of note, previous research examining the interaction between education, a prominent additional proxy measure of CR, and APOE genotypes regarding cognitive decline also revealed inconsistent results. Two studies (Seeman et al., 2005; Van Gerven et al., 2012) found the strongest cognitive decline in highly education APOE-ε4 carrier, while other studies showed no significant statistical interaction (Kalmijn et al., 1997) or a decreasing association of APOE-ε4 with cognitive decline as education increases (Shadlen et al., 2005). Only the latter finding is consistent with our results on the interaction of APOE-ε4 with the OCRS regarding cognitive decline in AgeCoDe. Potential explanations for inconsistencies should be investigated in future research. We will discuss one possible reason below in light of our results on the link between the OCRS and CR, BM, and BR (Section Implications).

Regarding the distinction between these resilience concepts, only suggestive indications can be derived in the absence of a direct assessment of pathology. Considering this, the pattern of our results on OCRS and APOE-ε4 statistical interaction effects on cognitive decline is most consistent with OCRS mainly acting through CR or BR since the OCRS mitigates the association between APOE-ε4 and cognitive decline. In contrast, the results are not consistent with the involvement of the OCRS in BM mechanisms, as an overall protective association with cognitive decline (as expected by BM theory) was not found.

OCRS and trajectories of cognitive decline aligned to dementia onset

Similarly, analyses of cognitive trajectories aligned with the onset of DAT support a link between the OCRS and CR, as we observed the expected longer preservation of cognitive function with a stronger decline afterward in those with higher OCRS. In contrast, BM would have predicted an earlier onset and, afterward, slower rate of decline in those with high OCRS. BR would have predicted no difference between individuals in the trajectories depending on the OCRS. Interestingly, similar trajectories have been found for the association of education, a well-known CR proxy, with cognitive decline before dementia onset (Amieva et al., 2014), emphasizing the feasibility of this approach to gain insights into the link between lifestyle factors and CR and related concepts. In addition, the stronger decline after the onset of impairment found in our study is consistent with previous research on CR effects in MCI patients (Myung et al., 2017). Nevertheless, the results derived from this approach should be considered suggestive evidence and require further investigation in cohorts with a direct assessment of pathology. Notably, in our study, the results obtained using this approach were consistent with the findings from DELCODE, providing a direct assessment of pathology. It is, therefore, tempting to speculate that studying cognitive trajectories aligned with dementia onset could provide a new opportunity to generate hypotheses on the most likely resilience mechanism in cohorts lacking a direct assessment of pathology. Since this would allow more cohorts and researchers to study resilience, it could help examine the generalizability and disparities in these concepts. However, more studies are needed to check whether the results from this approach reliably correspond to those obtained from analyses using direct assessments of pathology. Of note, change point models could provide another highly useful methodological approach to examine the onset and rate of change in cognition relative to dementia onset (Karr et al., 2018). These models have previously been successfully used to examine the effect of CR proxies on cognitive trajectories (Hall et al., 2007, 2009; Wilson et al., 2019b).

Implications

Our results suggest a stronger link between midlife cognitive activities, as indexed by the OCRS, and CR as compared to BM or BR. In line with these results, previous research on work-related cognitive activities in midlife has consistently shown a protective role in the risk of dementia and cognitive decline (Kröger et al., 2008; Smart et al., 2014; Pool et al., 2016; Then et al., 2017) beyond education. Similarly, higher levels of pathology (at the same level of cognitive function)

have been observed for individuals with more complex and cognitively demanding occupations, as suggested by the CR theory (Stern et al., 1995; Garibotto et al., 2008; Boots et al., 2015). No statistical interaction analyses were performed in these studies.

Of note, established proxy measures of CR show interactions with markers of pathology regarding cross-sectional cognition which are similar to the OCRS. For instance, higher education is associated with a reduced effect of amyloid pathology (Joannette et al., 2020) and white matter hyperintensities (Dufouil et al., 2003; Zahodne et al., 2019) on memory function. Early life cognitive abilities, as another proxy of CR, have been shown to attenuate the association of hippocampal with memory function in midlife (Vuoksimaa et al., 2013). However, not all studies found such an association for education (Malek-Ahmadi et al., 2017) or other reserve proxies (Vemuri et al., 2011).

Taken together, these results point to the relevance of stimulating midlife cognitive activities for dementia prevention. Importantly, several studies suggested prevention measures (Livingston et al., 2020), and, in particular, pharmacological interventions target a reduction in age-related pathologies. Cognitive activities in midlife, in turn, seem to promote CR (i.e., resistance to those pathologies), thereby contributing to dementia prevention through a complementary mechanism. Therefore, promoting cognitive activities in midlife should be considered as a complementary approach to early dementia prevention measures.

Furthermore, if (as our results suggest) midlife cognitive activities truly act through CR, their beneficial effect will be most pronounced in individuals at high risk for developing pathologic brain changes or in old age, where pathologic changes are highly prevalent. Future research on factors promoting CR in midlife should focus on these groups when assessing the suspected protective effects.

Future research should focus on refining specific interventions and activities that promote cognitive function and potentially CR-related mechanisms in midlife, since there are currently limited data to recommend conducting any specific cognitive activity or training to reduce dementia risk (Butler et al., 2018). Given that the OCRS captures occupational cognitive activities, it is tempting to speculate that enriching work environments, for example by proving regular advanced training offers, might positively affect cognition and CR.

While our results support a link between OCRS and CR in old age and individuals at elevated risk for AD, they do not exclude the possibility that the protective role of OCRS may be additionally conveyed by mechanisms other than CR. The OCRS might affect cognitive function by more than one resilience mechanism. Importantly, interactions between resilience mechanisms and differential sensitivity of our analyses to the specific hypotheses derived for each concept may have hampered links to resilience concepts beyond CR. Other lifestyle factors have been proposed to act through more than one mechanism (Arenaza-Urquijo et al., 2015; Chételat, 2018). Previous research has proposed that lifestyle factors may predominately act *via* neuroprotection (i.e., BM) in younger individuals or in the early phase of pathology accumulation, but then mainly act through CR as more pathology develops (Arenaza-Urquijo et al., 2015; Chételat, 2018). Therefore, the OCRS may show a different pattern of associations in other age strata or in other target populations. Interestingly, this hypothesis might explain why we could not completely replicate the results of Pool and colleagues (Pool et al., 2016) as the age at baseline in their study was considerably lower than that of AgeCoDe (Pool et al.: 26% ≥75 years vs. AgeCoDe: 100%≥75 years). Consequently, the higher age at baseline might have increased the power to detect the interaction of OCRS with APOE-ε4 in our study and reduced the likelihood of detecting the association with cognitive decline in the whole cohort. Systematic examination of the effect of age on the protective impact of lifestyle factors may provide additional valuable insights into the potential mechanisms conveying their effects.

Furthermore, our results on cognitive trajectories before dementia onset may have implications for the assessment of associations of CR-related factors in longitudinal cognitive data derived from cohorts enriched for individuals at risk for dementia, such as the memory clinic-based DELCODE cohort. In our AgeCoDe analyses, we observed that OCRS, as a potential marker of CR, was initially associated with a slower rate of cognitive decline. However, closer to the onset of dementia, it is associated with a faster rate of decline. Since the time to dementia onset is unknown for most memory clinic patients, our observation of predementia trajectories implies that time-dependent associations of CR markers may counteract each other in the longitudinal data and could cancel out. Similarly, when analyzing the interaction of CR markers with markers of pathology regarding longitudinal cognition, our results on predementia trajectories would imply that the direction of the interaction between CR and pathology markers will change nonlinearly over time, which is very difficult to model. However, in cross-sectional data, the influence of the time dependency of the association will be less severe because individuals with high CR should still show better cognition compared to individuals with lower CR close to dementia onset, despite a faster rate of decline. In line with this, we did not observe differential associations between changes in cognitive function and pathologic markers depending on the OCRS (modeled linearly) in the memory clinic-based DELCODE cohort (Supplementary Tables 9–11). Available sample size and limited follow-up on biomarker assessments precluded a more fine-grained assessment of the longitudinal, possible linear

interplay of the OCRS with pathology and cognition. Future research needs to assess whether the effects of the OCRS described in DELCODE are only restricted to processes acting early during the development of pathology (and might have manifested as baseline cognitive differences in DELCODE) or whether these processes are also important for later stages of pathologic changes.

Strengths and limitations

A strength of our study is the use of two independent cohorts that provide converging evidence from a large population-based study (AgeCoDe) and from a deeply phenotyped clinical cohort (DELCODE), with direct measures of certain pathologies. The hypotheses and operationalization generated for each of the research settings might be reused and adapted by future studies on other lifestyle factors and reserve proxies. Importantly, the statistical interaction effect of reserve proxies with markers of pathology on cognitive function has been proposed as the gold-standard test for CR (Stern et al., 2020) and has not been applied in most studies evaluating the link between midlife cognitive activities and CR. Of note, Udeh-Momoh et al. (2019) showed that a professional-level occupation reduces dementia risk associated with high levels of amyloid pathology and cortisol pointing toward a need to study the role of stress in the link between occupation and cognitive decline. Furthermore, our hypotheses derived for each resilience concept regarding trajectories of cognitive decline prior to the onset of dementia add a novel perspective. Such analyses may allow for future exploratory research in cohorts that lack a direct assessment of pathology. Moreover, replicating the results on the protective role of the OCRS, which was originally developed based on job characteristics in the USA, in two German samples, allowed us to demonstrate the generalizability of the results of the OCRS across societies and languages.

However, our study has some limitations. A direct assessment of pathology was missing in the AgeCoDe cohort, allowing only indirect and less precise tests of the links of the OCRS to BM and BR. Furthermore, our analyses of longitudinal changes in MRI markers in DELCODE were based on pre-processing procedures that considered different time points separately. Longitudinal MRI processing (Reuter et al., 2012), which is probably more sensitive to individual atrophy over time, would provide more certainty in definitely ruling out an association between OCRS and BM. Furthermore, the short follow-up duration in DELCODE has limited our sensitivity for the detection of age-related changes in CSF and MRI measures and might have hampered the detection of a link between OCRS and BM. In addition, sparse data on individuals with low levels of pathology and high OCRS in DELOCDE have limited our ability to reliably assess the association of OCRS with cognition in individuals without pathology. In addition, the cognitive task used in the population-based cohort might have been too insensitive to detect the effects of the OCRS conveyed by BM, that is, reduced accumulation of age-related pathology.

Moreover, we cannot show that the associations described are exclusively related to midlife cognitive activities. While the OCRS was developed to measure these activities, other (unmeasured) factors, such as socioeconomic status or general health and healthcare access, may have contributed to the association of the OCRS with CR in our cohort. Furthermore, from cross-sectional analyses, the directions of the effects underlying the observed associations are uncertain. For instance, individuals with more efficient brains may have worked in jobs involving more cognitive activities. However, regardless of the particular mechanism, high OCRS may serve as a marker for high CR. This might be helpful in defining effective and personalized prevention measures for individuals in future. Previous research has shown that cognitive and physical activity (Andel et al., 2015, 2016) can be more strongly associated with cognition and dementia risk reduction in individuals with less complex occupations.

Furthermore, the OCRS is based on general job characteristics from the O*NET database, which does not capture the individual work experiences and subjective perceptions of each participant. This may reduce the precision of the assessment of work-related occupational demands.

Conclusion

Our study demonstrates that high OCRS is associated with a reduced association of APOE-ε4 and AD biomarkers with cognitive decline and memory function, respectively. Furthermore, high OCRS is associated with a slightly later onset and steeper slope of cognitive decline prior to dementia. These results suggest that OCRS is a valid indicator of CR, a resilience mechanism that mitigates the effects of emerging pathology on cognitive functioning.

Data availability statement

The datasets presented in this article are not readily available because legal and privacy issues as well as ethical considerations do not allow making the data used in this study publicly available. However, access to the data can be granted by the data handeling center and the steering commitees of the AgeCoDe or DELCODE study for research purposes upon reasonable request. Requests to access the datasets should be directed to Luca.Kleineidam@ukbonn.de.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Commission of the Medical Association Hamburg, Ethics Committee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn, Medical Ethics Commission II of the Medical Faculty Mannheim/Heidelberg University, Ethics Committee at the Faculty of Medicine of the University of Leipzig, Ethical Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf, Ethics Committee of the Faculty of Medicine of the Technical University of Munich (AgeCoDe study). The DELCODE study was approved by the Ethical Committee of the medical faculty of the University of Bonn and approved by all participating sites Ethical Committees [Ethical Committee of the Charité Berlin, Ethical Committee of the medical faculty of the University of Bonn, Ethical Committee of the Univeristy of Cologne, Ethical Committee of medical faculty of the University of Göttingen, Ethical Committee of the Univeristy of Magdeburg, Ethical Committee of the Univeristy of LMU (Ludwig-Maximilians-University) Munich, Ethical Committee of the Univeristy of Rostock, Ethical Committee of the Univeristy of Tübingen]. The patients/participants provided their written informed consent to participate in this study.

Members of the AgeCoDe and AgeQualiDe study group

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Author contributions

LK conceptualized the study, conducted the statistical analyses, and drafted the manuscript. MW and SR-H contributed to the conceptualization and supervised the study. SWo and A-SW contributed to statistical analyses. A-SW, LZ, and SFo contributed to the acquisition, interpretation, and analysis of occupational data. LK, SWo, A-SW, LZ, SFo, SR, HBu, HK, BW, SWe, JWe, AF, MP, CBr, H-HK, DW, HBi, ML, FR, SFr, SE, CU, OP, ES, SA, AL, JP, KF, XK, ASc, CBa, BS, JWi, FM, WG, EI, MB, ED, KB, DJ, ME, B-SR, RP, IK, DG, ST, CL, MM, ASp, NR, FB, MH, AR, RY, MS, WM, FJ, SR-H, and MW substantially contributed to the acquisition and/or interpretation of the data. All authors reviewed and critically revised the manuscript for important intellectual content.

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Conflict of interest

ME receives research funding and consulting fees from Eli Lilly and Company.

The remaining 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.957308/full#supplementary-material

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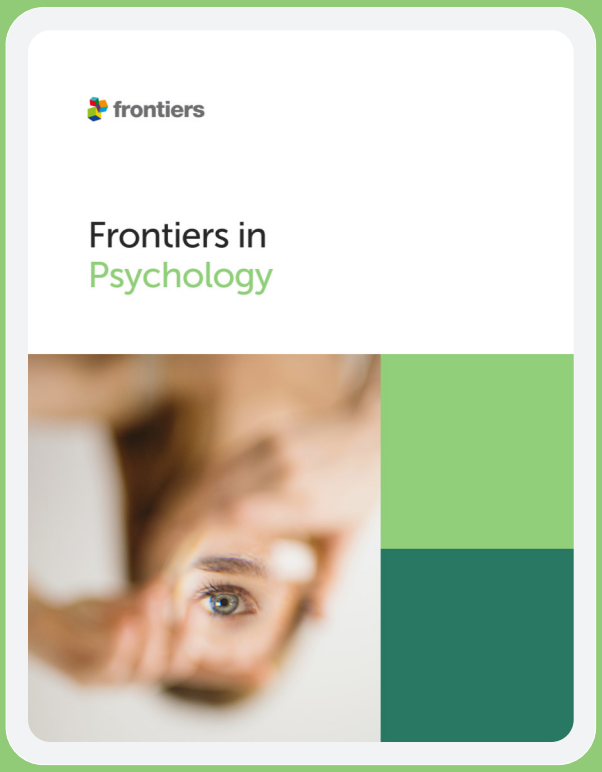

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