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SHORT REPORT

Theoretical frameworks and approaches used within the Reserve, Resilience and Protective Factors professional interest area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment

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Abstract

Introduction: Reserve, resilience, maintenance, and related concepts are intensely debated in aging and Alzheimer's disease research.

Methods: Through a short survey, we gathered information about theoretical concepts and methodologies used among research groups of the Reserve, Resilience, and Protective Factors Professional Interest Area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment.

Results: Overall 53 research groups responded. Reserve and resilience were the most frequently used conceptual frameworks. Education, occupation, leisure, and social activities were frequently used as measures, as were longitudinal designs. Neuropsychological assessments were almost universal, and usage of imaging biomarkers was frequent. In observational-epidemiological study designs, resilience and reserve together (vs reserve alone) were commonly used as theoretical frameworks.

Discussion: We provide a first description of concepts and methodologies used among reserve and resilience researchers. This will inform initiatives aiming to reach consensus on terminology and applications to establish common definitions.

KEYWORDS
brain reserve, cognitive reserve, maintenance, methodologies, outcome measures, resilience, techniques

1 | INTRODUCTION

Beginning with the recognition of the disconnect between pathology and cognition in aging and dementia,[1] the field of reserve, resilience, and protective factors has evolved tremendously. The first theoretical frameworks included concepts such as brain reserve capacity[2] or cognitive reserve versus brain reserve,[3] which have been instrumental in propelling the research into inter-individual differences that allow some people to cope better with aging and disease. In the cognitive aging field, several models aiming to explain inter-individual differences have also emerged.[4,5] Through autopsy[6] and biomarker-based investigations of Alzheimer's disease (AD) patients, our understanding of these processes has evolved across the years.

The recent biological definition of AD, acknowledging a long preclinical phase of the disease[7] and the emergence of specific biomarkers (cerebrospinal fluid [CSF] and neuroimaging[8,9]) have allowed further study of individual differences regarding the factors and mechanisms responsible for the stability of cognitive and clinical function, despite evident neuropathology.[10] These observations have led to novel terms and concepts including resistance and resilience to describe the pathology–cognition mismatch.[11,12] The rapid turnover of ideas and theoretical frameworks has led to recent consensus statements, aiming to integrate the definitions and the study of brain mechanisms underlying concrete concepts.[4,13] Further, initiatives such as the National Institute on Aging (NIA)-supported Collaboratory on Research Definitions (https://reserveandresilience.com/) have been funded to support workshops as a platform to exchange ideas and develop operational definitions.

We aimed to describe the most common conceptual frameworks, terminologies, experimental designs, outcome variables, and specific techniques used among researchers working in this field. For this, we conducted a survey within the Reserve, Resilience and Protective Factors professional interest area (PIA) of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) and present the results as part of this work.

2 | METHODS

During the Alzheimer's Association International Conference (AAIC) 2018 held in Chicago (Illinois, USA), the Reserve, Resilience and Protective Factors PIA discussed a proposal to collect information about the theoretical backgrounds and methodological approaches commonly used by ISTAART members. At a subsequent meeting, the executive committee agreed to undertake this initiative as part of the PIA's activity.

Survey data collection was completed between October 2018 and April 2020. In September 2018, the Executive Committee reached a consensus regarding relevant items and questions of the survey, which were planned as non-mutually exclusive fixed responses, but also leaving some open fields (see Table 1 and supporting information). By October 2018, the survey was formatted into a web-based platform by the Alzheimer's Association ISTAART and sent out to all PIA members. The first wave of responses had a total of 30 identifiable research groups working within the field complete the surveys. Between May and July 2019, and in September 2019, after the first workshop on research definitions of the Reserve & Resilience meeting held in Bethesda, Maryland, USA, further individual group responses were collected. A final round was undertaken using the PIA social media channels (LinkdIn [PIA group] and PIA hashtag #ReservePIA) during March and April 2020.

3 | RESULTS

The present survey reports responses of 53 clinical and research teams. In terms of geography, 23 groups represented eight different European countries, 21 were from the USA or Canada, 4 were from South America, 3 from Australia, 1 from China, and 1 from India (Figure 1A).

3.1 | Theoretical model/concept framework and examples of research findings

Most groups (84.9%) indicated that the term "reserve" best defined their current research activity. The concept of resilience was the second most commonly addressed (66% of the teams) followed by the use of maintenance (50.9%) and neuroprotection (39.6%; Figure 1B).

3.2 | Determinants and mechanisms of reserve and resilience

We asked participants about potential determinants of cognitive reserve. Up to 86.8% of participants answered that they considered environmental determinants, but the majority of teams also consider genetic aspects (50.9%) and to a lesser extent investigated gene–environment approaches (35.8%). The high frequency of considering

TABLE 1 Specific questions included in the survey

Group identification
Key members
Institution
Theoretical framework
What is the theoretical model/concept framework that best defines your group's research work?
Specific aspects of cognitive reserve
Determinants of Cognitive Reserve tick box:
☐ Environmental
☐ Genetic
☐ E X G
If not, please specify…
☐ Mechanisms of Reserve, tick box:
☐ Biological
☐ Psychological
☐ Psychosocial
If not, please specify…
☐ Clinical outcomes of Cognitive Reserve, tick box:
☐ Cognitive status
☐ Cognitive decline
☐ Incidence of dementia
☐ Incidence MCI
Key measures
☐ Classical Cognitive Reserve measures (education, occupation, social, leisure)
☐ Residual approaches etc.
Methods employed
Study designs, tick box:
☐ Observational-Epidemiologic
☐ Longitudinal
☐ Experimental
☐ Brain series
☐ RCT
☐ Animal models If not, please specify
Specific Techniques, tick box:
☐ Neuropsych
☐ CSF and imaging biomarkers
☐ Autopsy studies
If not, please specify
Top 3-5 findings and relevant references, also please feel free to provide a link to your website or Pubmed search for relevant publications

Abbreviations: CSF, cerebrospinal fluid; MCI, mild cognitive impairment; RCT, randomized controlled trial.

environmental determinants of reserve appears to be aligned with key measures used to study reserve and resilience. Here, most reported (84.9%) that they termed the measures as "classical" from the CR reserve theory (ie, independent or composite scores of education, occupation, social, and leisure activities; Figure 1C).

With regard to the mechanisms underlying the general concept of reserve (ie, irrespective of the theoretical approaches selected), most groups focused their activity on the biological mechanisms (86.8%), which were often combined with psychological (67.9%), psychosocial (54.7%), or the consideration of all three kinds of mechanisms (37.7%).

3.3 | Research study designs and methodologies

Most groups claimed they were currently engaged in observational–epidemiologic investigations (75.5%), and in particular in longitudinal studies (84.9%), and fewer were conducting experimental studies (37.7%), brain series/autopsy investigations (26.4%), or randomized clinical trials (22.6%). Only one group was conducting reserve and resilience–related research on animal models. The high prevalence of groups engaged in longitudinal studies is probably reflective of the fact that most of them indicated that they considered cognitive decline (96.2%) in their study designs with lower percentage of groups working on incidence of mild cognitive impairment (MCI; 45.3%) or dementia (43.4%) as primary outcomes (Figure 1D). Concerning the main techniques used, most investigations include neuropsychological assessments (88.7%), and frequently consider imaging (75.5%) as well as CSF markers (54.7%) data (Figure 1E).

We finally investigated whether the two main frameworks, namely reserve and resilience, were associated with distinct study designs, clinical outcomes, main measures, and principal techniques. To investigate this, we compared the responses of those groups that had indicated that their main conceptual model was reserve but did not include resilience (N = 12), to those groups that included resilience (N = 36; all but four including reserve too). Those groups that had selected resilience as a theoretical framework more frequently used observational–epidemiological study designs (Figure 2A; Fisher's exact test: 8.15, $P < .005$). They also appear to include more frequently a "biological component" in their techniques (ie, CSF), key measures (ie, biological) or study designs (ie, brain series), as well as mental health status as key measures (Figure 2A-D); however, formal testing did not reveal significant differences (not shown).

4 | DISCUSSION

Here, we surveyed and present an overview of the concepts and methodological approaches currently used by groups mainly pertaining to the Resilience and Protective Factors' PIA of ISTAART. This survey captured the breadth of the theoretical model/concept framework and determinants/approaches that are used in our

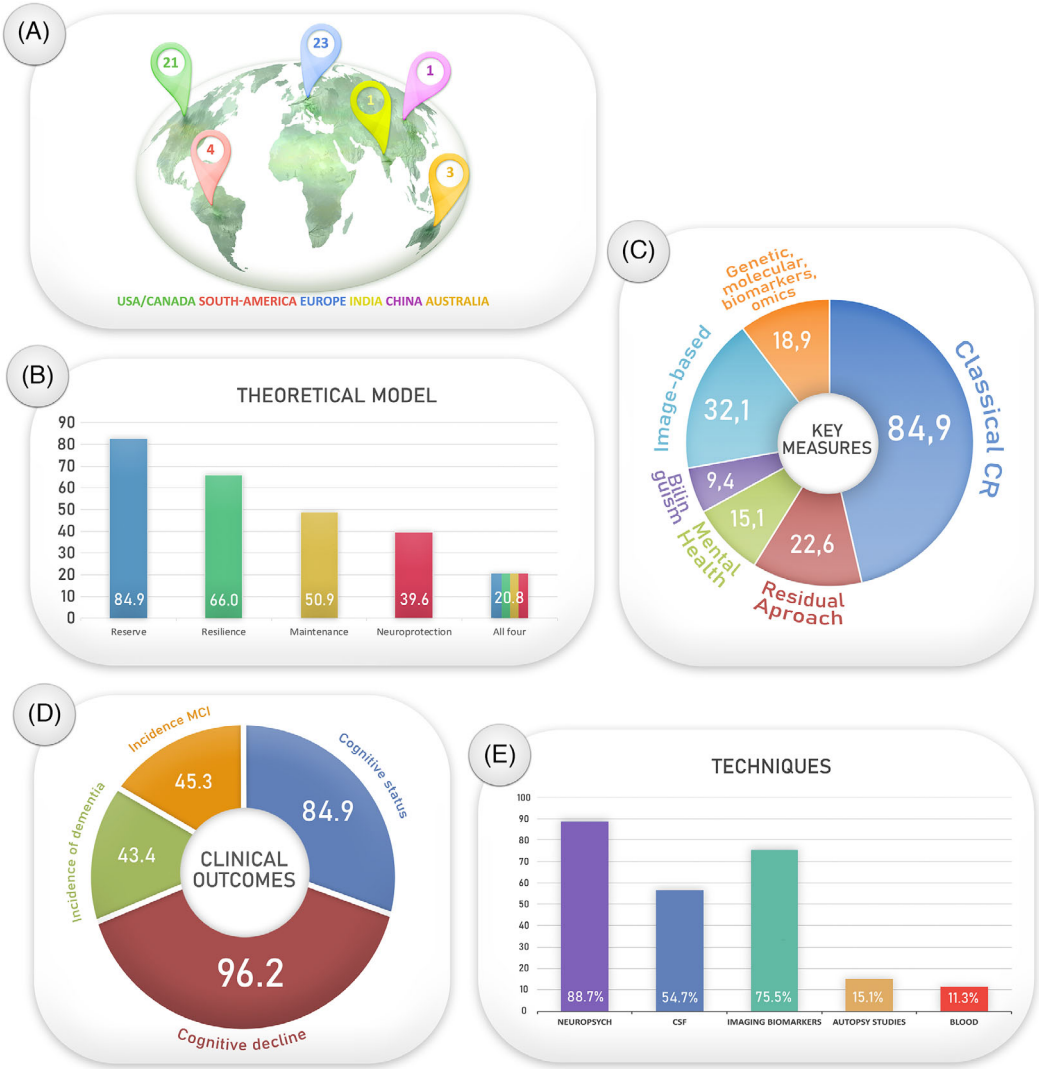

FIGURE 1 Graphical representation of responses obtained to the survey questions. A, World globe figure with the distribution of the N = 53 groups responding per continent/ main region. B, What is the theoretical model/concept framework that best defines your group's research work? C, "Key measures" classical CR measures (education, occupation, social, leisure) residual approaches, etc. D, Clinical outcomes of Cognitive Reserve tick box: Cognitive status, Cognitive decline, Incidence of dementia, Incidence MCI (mild cognitive impairment). E, Specific Techniques tick box: Neuropsych CSF (cerebrospinal fluid) and Imaging Biomarkers, Autopsy Studies. If not, please specify. Values represent percent of responses. Within each item, responses were not mutually exclusive (ie, more than one answer per item was allowed)

research area and also highlights the opportunity present in unifying the language across research groups and methodologies.

Present findings indicate that the term reserve is the most frequently used in AD research. However, the concept of resilience is also commonly incorporated. It should be noted that according to current conceptual definitions,[3] resilience refers to a more general term that aggregates multiple reserve-related processes. In the overall sample, more than 20% of professionals use all four main concepts (reserve, resilience, maintenance, neuroprotection) in their research. A comparison between groups that used the term resilience versus reserve (without resilience) showed similar use of methodologies, techniques, clinical outcomes, or general study designs, except for the fact that they tended to be more frequently engaged in observational–epidemiological studies. Whether the resilience term is more frequently associated with the use of "biological" or mental health aspects (personality, stress, psychoaffective states, Figure 2A, B, and D) should be addressed in follow-up investigations.

Most of our respondents focus on the study of environmental determinants of reserve followed by genetic aspects and consider classical measures within neuropsychological and neuroimaging investigations. Finally, we noted that a large percentage of respondents informed that they were engaged in longitudinal studies, which due to their advantages over cross-sectional designs[14] appears to be a prevalent approach. This may also be related to the fact that "cognitive decline" was one of the main outcomes used by PIA members and that it is the design of choice to investigate protective mechanisms.[3]

Biomarkers were widely used across all research groups reflecting the emergence and increased use of in vivo measurements in AD. More

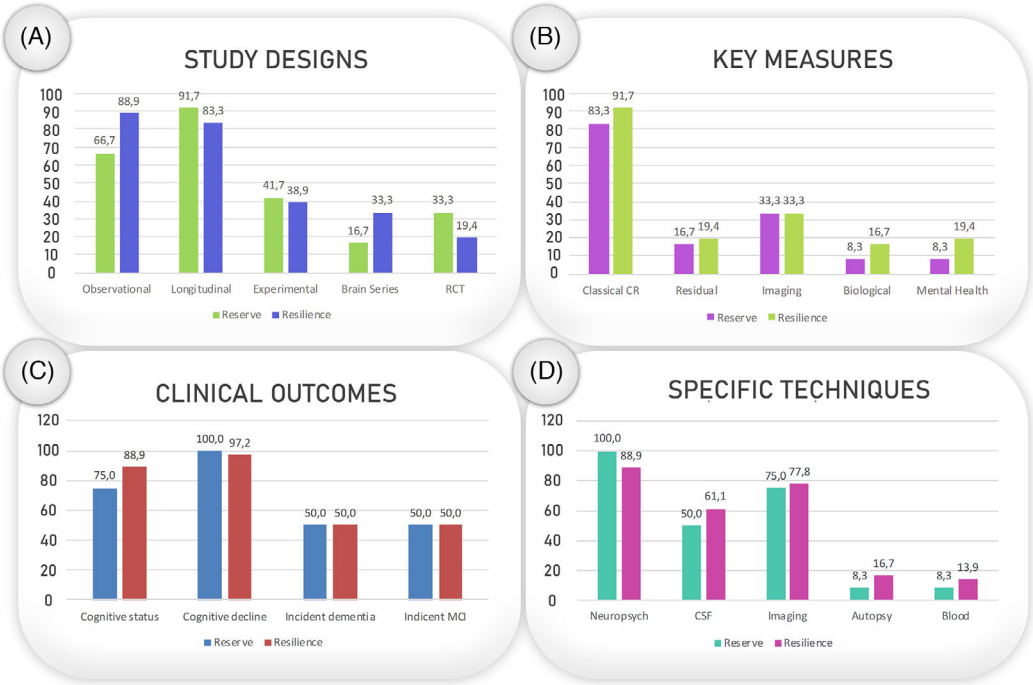

FIGURE 2 Visual comparison of responses between the groups that included reserve as a main theoretical framework but excluded resilience (N = 12) versus those including this latter term in their definitions (N = 36). Survey questions: (A) Study designs tick box: Observational-Epidemiologic, Longitudinal, Experimental, Brain series, RCT, Animal models, If not, please specify; (B) "Key measures" Classical Cognitive Reserve measures (education, occupation, social, leisure) Residual Approaches etc.; (C) Clinical outcomes of Cognitive Reserve tick box: Cognitive status, Cognitive decline, Incidence of dementia, Incidence MCI (mild cognitive impairment); and (D) Specific Techniques tick box: Neuropsych CSF (cerebrospinal fluid) and Imaging Biomarkers, Autopsy Studies, If not, please specify. Values represent percent of responses. Within each item, responses were not mutually exclusive (ie, more than one answer per item was allowed)

than 50% of groups used CSF-based markers and >75% used "imaging biomarkers." This latter term was not further specified in the survey, although some groups designated that they were using "PET [positron emission tomography]-based biomarkers," to be in accordance with the relevance of molecular imaging markers in the discipline.[15,16] Altogether and provided the high prevalence of groups stating that they use "neuroimaging" information, either as key measures or specific techniques, a future detailed survey should include more fine-graded questions about the particular PET tracers or magnetic resonance imaging (MRI) sequences they use in their research. Finally, other professionals specifically stated they were using blood-based information, which also likely reflects the advent of these biomarkers in the AD research field[17] and which should also be assessed in more detail in further versions of the survey.

In summary, this report represents a first survey of the terms and methodologies used by the Reserve, Resilience and Protective Factors PIA. Repeating this type of questionnaire in the future may be useful to measure how the focus of professionals' work within the area, as well as the use of emerging technologies, evolve in response to the progressive incorporation of new consensus on theoretical and empirical research within the field.

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CONFLICTS OF INTEREST

The authors do not report any relevant conflicts related to this manuscript submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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