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WYLLIANS JOSE VENDRAMINI BORELLI

CORRELAÇÃO ENTRE NEUROIMAGEM MOLECULAR, ESTRUTURAL E FUNCIONAL EM SUPERIDOSOS

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PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
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Tese de Doutorado

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Tese apresentada como requisito parcial para obtenção do grau de Doutor pelo Programa de Pós-Graduação de Medicina e Ciências da Saúde da Pontifícia Universidade Católica do Rio Grande do Sul.

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Para minha mãe, meu pai e minha irmã,
Ao apoio incondicional, ao suporte incansável e à inspiração constante nessa jornada.

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E a todas pessoas que passaram pela minha vida, de forma temporária ou permanente. Esse trabalho significa muito mais do que um requisito para o título; significa eternizar os quatro anos de maior aprendizado da minha vida.

“Cogito, ergo sum”.

René Descartes

APRESENTAÇÃO

Essa tese está organizada em três **partes,** cada uma constituída dos seguintes itens:

Parte I: Resumo, Resumo em língua inglesa, Abreviações, Introdução e Objetivos;

Parte II: Métodos e Estudos relacionados à tese;

Parte III: Conclusão, Anexos e Referências bibliográficas.

Nos anexos foram incluídos os *instrumentos de avaliação* utilizados na coleta de dados (Anexos C, D, E, F), assim como os *trabalhos em congressos* resultantes da tese (Anexo G), e o *impacto social* desse projeto (Anexo H). Também foram incluídos os *artigos realizados durante o período de doutoramento* não relacionados diretamente com o tema da tese (Anexo I).

Sumário

PARTE I

Resumo

Borelli, Wyllians Vendramini. **Correlação entre neuroimagem molecular, estrutural e funcional em Superidosos**. Tese de Doutorado, Programa de Pós-Graduação em Medicina e Ciências da Saúde: Clínica Médica, Pontifícia Universidade Católica do Rio Grande do Sul. Porto Alegre, Brasil, 2019.

Superidosos (SI) são indivíduos de 80 anos ou mais, com memória semelhante a indivíduos mais jovens. Esses idosos possuem características cerebrais únicas, como maior espessura do cíngulo anterior e conectividade funcional aumentada nessa região. Neste estudo, analisamos os Superidosos através de neuroimagem multimodal através de PET com [^{18}F]Fluorodeoxiglicose (FDG), [^{11}C]Pittsburgh Compound B (PIB), Ressonância Magnética funcional (RMf) e Ressonância Magnética estrutural (RMe). Indivíduos da comunidade foram avaliados com uma bateria cognitiva e classificados em 4 grupos. SI foram definidos como indivíduos com escores de memória episódica semelhante a indivíduos de 50 a 65 anos e outros testes dentro do esperado para idade e escolaridade; Controles idosos (C80) foram idosos de 80 anos ou mais com escores cognitivos normais para idade. Controles meia-idade (C50) foram indivíduos entre 50 e 65 anos, com escores cognitivos normais para a idade. Esse estudo também incluiu um grupo com Doença de Alzheimer para fins comparativos, mas não para a análise. Após, foi mensurada atividade metabólica (PET-FDG), depósito de placa amiloide (PET-PIB), conectividade funcional (RMf), e espessura cortical e volumetria (RMe) da amostra. Foi analisada a relação entre os escores cognitivos e áreas do cíngulo e hipocampo. O grupo SI demonstrou maior atividade metabólica na região subgenual esquerda do córtex do cíngulo anterior quando comparados com o grupo C80 (sACC, $p < 0,005$). O acúmulo amiloide foi similar entre SI e o grupo C80. O grupo SI também apresentou menor conectividade entre o sACC esquerdo e o cíngulo posterior esquerdo. Esses achados indicam o papel central do ACC em SI, mesmo na presença de patologia amiloide. Eles também sugerem que sACC pode ser usado como potencial biomarcador de memória em idosos.

Palavras-chave: Idosos de alta performance; Doença de Alzheimer; RM; PIB; FDG

Abstract

Borelli, Wyllians Vendramini. **Correlation between molecular, structural and functional neuroimaging in Superagers.** Ph.D. dissertation, Post-graduate program in Medicine and Health Sciences: Clinical medicine. Pontifical Catholic University of Rio Grande do Sul. Porto Alegre, Brazil, 2019.

SuperAgers (SA) are older adults at 80 years or above with memory similar to middle-aged adults. These older adults exhibit unique brain features, such as increased cortical thickness of the anterior cingulate cortex and increased functional connectivity within the same region. In this study, we analyze SuperAgers through multimodal neuroimaging using PET with [^{18}F]Fluorodeoxiglicose (FDG) and [^{11}C]Pittsburgh Compound B (PIB), functional MRI (fMRI) and structural MRI (sMRI). Community-dwelling individuals were evaluated with a broad cognitive battery and then classified in 4 groups. SA were defined as individuals at or above 80 years of age and delayed-memory scores similar to middle-aged adults between 50 to 65 years-old, while non-memory tests within the normal range for age. Age-matched Controls (C80) were defined as older adults cognitively normal for age. Middle-aged controls (C50) were defined as individuals between 50 to 65 years-old, cognitively normal for age. All individuals underwent the neuroimaging protocol to measure metabolic activity (PET-FDG), amyloid deposition (PET-PIB), functional connectivity (fMRI), cortical thickness and volume (sMRI). The relationship between cognitive scores and cingulate areas and hippocampus were examined. The SA group showed increased FDG SUVr in the left subgenual Anterior Cingulate Cortex (sACC, $p<0.005$) as compared to that in the C80 group. Amyloid deposition was similar between SA and C80 in the described regions or overall areas ($p>0.05$). The SA group also presented decreased connectivity between left sACC and posterior cingulate ($p<0.005$) as compared to that of C80 group. These results support the key role of ACC in SA, even in the presence of amyloid deposition. It also suggests that sACC can be used as a potential memory biomarker in older adults.

Key words: High-performing older adults; Alzheimer's Disease; MRI; PIB; FDG

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LISTA DE ABREVIATURAS E SIGLAS

PIB	[^{11}C]Pittsburgh Compound B
FDG	[^{18}F]Fluorodesoxiglicose
βA	Proteína β-amiloide
ACE-R	*Addenbrooke's Cognitive Evaluation - Revised*
ADNI	*Alzheimer's Disease Neuroimaging Initiative*
aMCC	*anterior Midcingulate*
BNT	*Boston Naming Test*
BOLD	*Blood-oxigen-level dependent*
C50	Grupo Controle Meia-idade (50-60 anos)
C80	Grupo Controle Idosos (80 anos)
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CCL	Comprometimento cognitivo leve
CFT	*Category Fluency Test*
CT	*Computed tomography*
DA	Doença de Alzheimer
DM	Difusividade Média
DS	*Digit Span*
DTI	*Diffusion tensor imaging*
FA	*Fractional Anisotropy*
FAQ	*Functional Assessment Questionnaire*
FDA	*Food and drug administration*
FOV	*Field of View*
GDS-15	*15-item Geriatric Depression Scale*
HAROLD	*Hemispheric Asymmetry Reduction in Older Adults*
MoCA	*Montreal Cognitive Assessment*
PASA	*Posterior-Anterior Shift in Aging*
PET/CT	*Positron emission tomography / Computed Tomography*
pMCC	*posterior Midcingulate*
prACC	*pregenual Anterior Cingulate Cortex*
PSEN	Gene da preselina
PUCRS	Pontifícia Universidade Católica do Rio Grande do Sul

RAVLT	*Rey Auditory Verbal Learning Test*
RAVLT-A7	*Rey Auditory Verbal Learning Test* – Lista A7
RM	Ressonância magnética
RMf	Ressonância magnética funcional
rsfMRI	r*esting state functional Magnetic Resonance Imaging*
STAC	*Scaffolding Theory of Aging*
SNC	Sistema Nervoso Central
Tau-t	Proteína tau total
Tau-p	Proteína tau fosforilada
TCLE	Termo de Consentimento Livre e Esclarecido
TE	*Time Echo*
TMT-A	*Trail-Making Test A*
TMT-B	*Trail-Making Test B*
TR	*Time Repetition*

1 INTRODUÇÃO

1.1 O PROCESSO DE ENVELHECIMENTO

Processo natural de todos os seres vivos, a morte é decorrente da vida. O ciclo vital se caracteriza pelo progressivo declínio funcional das diversas unidades do corpo humano, de maneira irreversível e indistinta (KIRKWOOD, 2008). O processo do envelhecimento afeta todos os órgãos do corpo, embora de modo e intensidade diferentes. De modo global, destacam-se a perda de agilidade do ritmo fisiológico (MORAES, 2008), a lentificação do metabolismo e a inflexibilidade dos sistemas (DE GAUDIO et al., 2009; VELDHUIS, 1997). Os órgãos, portanto, demonstram sinais de "perda de complexidade" (LIPSITZ; GOLDBERGER, 1992), conceito que engloba praticamente todas as mudanças que ocorrem no envelhecimento e possui interessante relação com o sistema nervoso central (SNC).

Ao nível biológico, o envelhecimento é o acúmulo gradual de dano molecular e celular (VASTO et al., 2010). Os neurônios parecem sofrer particular efeito biológico do tempo: regiões com alta plasticidade sináptica são mais vulneráveis ao envelhecimento (FJELL et al., 2014). A morte neuronal decorrente do envelhecimento afeta principalmente neurônios longos do córtex cerebral e cerebelar (DORSZEWSKA, 2013), levando também à perda de conexões dendríticas, diminuição global de sinapses e perda de volume total (HAUG; EGGERS, 1991).

1.1.1 Epidemiologia do envelhecimento

Indubitavelmente, a população mundial está em franco envelhecimento. Segundo a Organização Mundial de Saúde, cerca de 901 milhões de pessoas acima de 60 anos vivem atualmente no mundo (UNITED NATIONS, DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, 2015). Só no Brasil, esse número atingiu 24 milhões em 2015, com projeção para 69 milhões de indivíduos acima de 60 anos em 2050. Atualmente, os idosos representam 14,3% da população brasileira, com porcentagem ainda maior no sul do país (IBGE, 2016). No Brasil e outros países em desenvolvimento, estima-se que essa população aumente em até 71% nos próximos 15 anos, uma taxa maior que dos países do hemisfério norte (23-41%).

Em decorrência dessa transição demográfica, um grupo previamente pouco frequente passa a ser objetivo de estudo: os longevos. Esses idosos atingem idade avançada, geralmente 80-85 anos ou mais de acordo com o país (CAMPION, 1994; ROSSET et al., 2011), e estão cada vez mais presentes na sociedade atual. Estima-se que o número de longevos no mundo passe de 125 milhões em 2015 para 434 milhões dentro dos próximos 50 anos (UNITED NATIONS, DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, 2015). Essa transição

demográfica alterou dramaticamente a estrutura da sociedade. O aumento da população geriátrica elevou a prevalência de comorbidades, da necessidade de cuidadores e de instituições especializadas (KNICKMAN; SNELL, 2002). O conceito de autonomia e funcionalidade é cada vez mais valorizado e uma meta importante dos cuidados na saúde do idoso.

1.1.2 Funcionalidade em idosos

A funcionalidade no idoso começou a ser estudada em contraste ao estigma de que o envelhecimento é associado à morbidade e perda de autonomia (ARAÚJO; COUTINHO; SANTOS, 2006). Rowe e Kahn originaram o termo "Envelhecimento Bem-Sucedido", valorizando o estudo de idosos cuja capacidade funcional permanece estável apesar do envelhecimento (Fig. 1) (ROWE; KAHN, 1987, 1997). Essa definição é multidimensional e engloba não apenas a ausência de doenças e incapacidades, mas também a manutenção de funcionamento físico e cognitivo – mantendo a sociabilidade e a produtibilidade (BOWLING, 2005). É notável a necessidade de uma posição ativa perante a vida, além da simples ausência de patologia. Os autores também citam o papel do bom funcionamento cognitivo para a independência e autonomia de um indivíduo, principalmente a escolaridade (ROWE; KAHN, 1997). O funcionamento cognitivo pode ser mensurado através de diferentes testes neuropsicológicos, com papel importante na avaliação de sinais e sintomas clínicos.

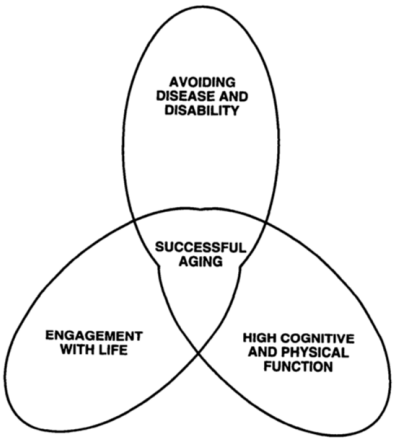

Figura 1. Representação gráfica dos três pilares necessários para o Envelhecimento Bem-Sucedido. Fonte: (ROWE; KAHN, 1997).

1.1.3 Funções cognitivas no envelhecimento

A memória é um domínio particularmente importante no processo de envelhecimento. Ela é composta por três mecanismos de funcionamento: consolidação (ou aquisição), armazenamento e evocação. Apesar de ser um assunto em constante debate, a memória pode ser dividida em imediata, de curto-prazo e de longo-prazo (Fig. 2), esta última subdividida em

declarativa (episódica e semântica) ou não-declarativa (procedural, *priming*, entre outros)(ATKINSON; SHIFFRIN, 1968). Enquanto a memória imediata, por definição, dura alguns segundos, a memória de curto-prazo (sobreposta ao conceito de memória de trabalho) dura minutos e é usada para manter e manipular informações úteis em outras tarefas cognitivas complexas. A memória de longo-prazo declarativa episódica é composta por lembranças e eventos autobiográficos (TULVING, 2002), enquanto a declarativa semântica refere-se a fatos e conhecimentos gerais; diferentemente, a memória de longo-prazo não-declarativa inclui procedimentos sensoriomotores, habilidades cognitivas, hábitos, *priming* (memória implícita em que um estímulo influencia a resposta), condicionamento, habituação e sensibilização (HENKE, 2010). Diferentemente desses processos, a memória de trabalho possui papel operacional (BADDELEY, 1983) e é parte de funções executivas.

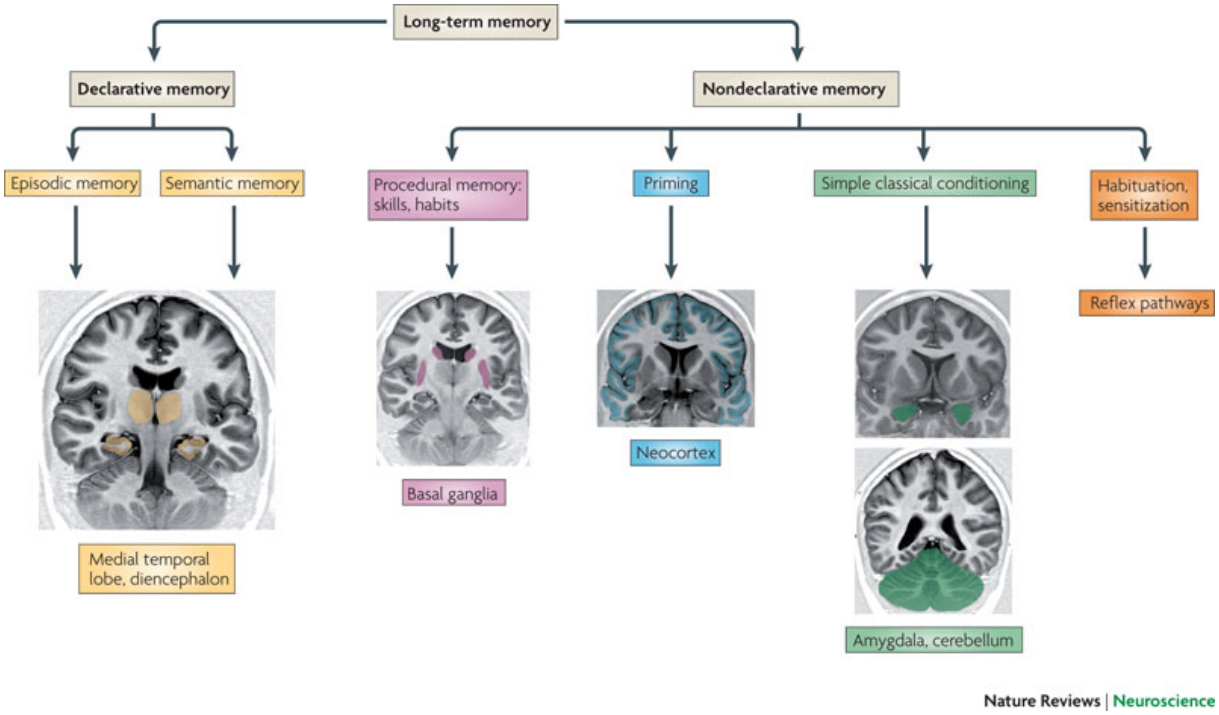

Figura 2. Classificação dos subtipos de memória. A memória declarativa é dividida em memória episódica ou semântica, ambas com forte ativação do lobo temporal medial em estudo funcional. A memória não-declarativa é constituída da ativação dos gânglios basais, neocortex, amígdala e cerebelo. Fonte: (HENKE, 2010).

O envelhecimento afeta os processos cognitivos de maneira distinta. Algumas funções apresentam declínio ao longo da vida, como velocidade de processamento, memória de trabalho e aquisição de memória episódica (HARADA; NATELSON LOVE; TRIEBEL, 2013; HEDDEN; GABRIELI, 2004). Em seguida, o declínio afeta a atenção, a habilidade de executar multitarefas e a solução de problemas. A perda da memória semântica e de vocabulário ocorrem

mais tardiamente, tipicamente após os 70 anos. No entanto, a memória autobiográfica e o processamento emocional parecem permanecer estáveis ao longo dos anos.

Uma característica marcante encontrada nos estudos em gerontologia é a grande variabilidade cognitiva nos idosos (HARADA; NATELSON LOVE; TRIEBEL, 2013). Essa diferença supostamente ocorre por três fatores principais: a influência genética, a influência do meio e os desenhos experimentais estudados. A carga genética é descrita como determinante de cerca de 60% da variação de performance em testes cognitivos (BOUCHARD; MCGUE, 1981). O restante é explicado por experiências acumuladas e à exposição a diferentes contextos ao longo da vida, com impacto fisiológico, psicológico e biológico nas funções cognitivas (TUCKER-DROB; BRILEY; HARDEN, 2013). É importante levar em consideração os potenciais vieses gerados por estudos transversais e estudos longitudinais. Avaliações pontuais podem superestimar o efeito de alta performance, pois exigem que os idosos se voluntariem, enquanto análises longitudinais podem subestimar efeitos relacionados a idade, principalmente por efeitos práticos e atrito (HEDDEN; GABRIELI, 2004; SCHAIE; WILLIS, 2010).

A diferenciação entre envelhecimento normal ou patológico é de fundamental importância na avaliação clínica. O declínio cognitivo é apontado atualmente como consequência de alterações neurobiológicas tanto no envelhecimento quanto no processo demencial (DONOHUE et al., 2017; GRADY, 2008). A avaliação clínica, portanto, não oferece um bom alvo terapêutico, pois são fenótipos tardios de mecanismos subjacentes. Um compilado de estudos recentes corrobora esse fato, dado que 99% de todas terapias recentes para a Doença de Alzheimer (DA) falham em cessar ou reverter a sua progressão (CUMMINGS; MORSTORF; ZHONG, 2014). É colocado em cheque o quanto ainda resta descobrir do processo fisiopatológico dessa doença, e novos alvos terapêuticos se fazem necessários. Nesse contexto, o estudo de agentes patológicos continua sendo essencial, porém o processo de envelhecimento cognitivo saudável ganhou significante foco recentemente (DEPP; HARMELL; VAHIA, 2012; EYLER et al., 2011).

1.2 ENVELHECIMENTO COGNITIVO BEM-SUCEDIDO

O envelhecimento bem-sucedido é direcionado a fatores determinantes da *funcionalidade* em idosos. Complementando a necessidade de autonomia proposta neste conceito, Depp e Jeste propuseram a definição de “envelhecimento *cognitivo* bem-sucedido” a fim de enfatizar o papel essencial da cognição no envelhecimento (DEPP; VAHIA; JESTE, 2010).

Diversas funções cognitivas são reconhecidas com papel fundamental no processo de envelhecimento saudável (FIOCCO; YAFFE, 2010). O prejuízo cognitivo mostrou forte poder preditivo de institucionalização em um estudo populacional (AGÜERO-TORRES et al., 2001) e pior prognóstico em longevos (TAKATA et al., 2014). A cognição também foi associada a importante componente da qualidade de vida e autonomia individual (NEALE et al., 2001) e impacta diretamente as atividades instrumentais de vida diária do idoso (WILLIS et al., 2006). A trajetória do envelhecimento cognitivo é um *continuum* que abrange desde o declínio patológico até a manutenção cognitiva (Fig. 3) (NYBERG et al., 2012). No extremo oposto das patologias demenciais situam-se os indivíduos com preservação da capacidade cognitiva, ainda hoje sem consenso acerca de terminologia mais apropriada. Acredita-se que esses sujeitos teriam mecanismos cerebrais intrínsecos capazes de minimizar as consequências dos processos patológicos, mas atualmente as teorias cognitivas não explicam o mecanismo de sua performance.

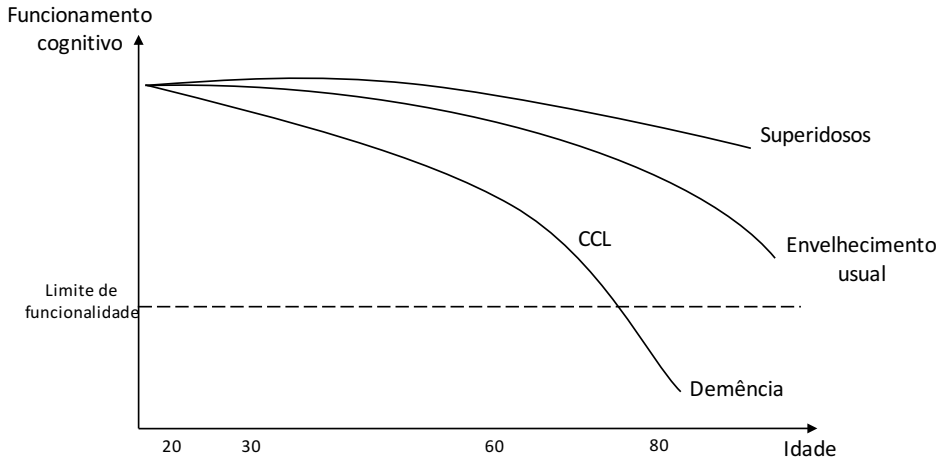

Figura 3. Trajetórias do envelhecimento cognitivo. Indivíduos com menor efeito do declínio cognitivo são denominados Superidosos. Fonte: (BORELLI et al., 2018a).

1.2.1 Teorias do envelhecimento cognitivo

Diversas teorias de envelhecimento cognitivo foram criadas na tentativa de melhor entender o processo de envelhecimento. Entre elas, destacam-se: teorias de compensação, teorias de reserva e teorias de manutenção (CABEZA et al., 2018).

As teorias de compensação baseiam-se no fato de que idosos normais apresentam hipofuncionamento cerebral regional. Segundo essas teorias, é necessária uma ativação cerebral compensatória para sobrepor os efeitos das regiões cerebrais hipofuncionantes. Os modelos HAROLD (Hemispheric Asymmetry Reduction in Older Adults) e PASA (Posterior-Anterior Shift with Aging) citam a utilização de vias não-tradicionais como alternativa compensatória

ao envelhecimento para manter o funcionamento cognitivo (CABEZA, 2002; DAVIS et al., 2008). Esses modelos elucidam a maior utilização de ambos hemisférios como alternativa à perda funcional e com a menor utilização de estruturas posteriores em idosos normais, respectivamente (BERLINGERI et al., 2013). Na mesma linha, o modelo STAC (*Scaffolding theory of Aging and Cognition*) propõe vias compensatórias como mecanismo de evitar o declínio cognitivo (PARK; REUTER-LORENZ, 2009).

O modelo de reserva foi proposto para explicar a discrepância entre o nível de patologia cerebral e suas consequências funcionais ou cognitivas (Fig. 4) (STERN, 2009). Mais especificamente, a reserva cerebral é a susceptibilidade do indivíduo sofrer dano cerebral como função da (a) extensão do processo patológico e (b) da medida quantitativa da capacidade de reserva cerebral (tamanho cortical, número de neurônios e sinapses, ...) (BARULLI; STERN, 2013). Já a reserva cognitiva é um conceito mais ativo que a reserva cerebral, pois leva em consideração a variabilidade individual pela experiência de vida, a atividade neural e a atividade compensatória envolvida. Ambos os conceitos são muito próximos e envolvem a atividade compensatória como mecanismo de manter a performance cognitiva.

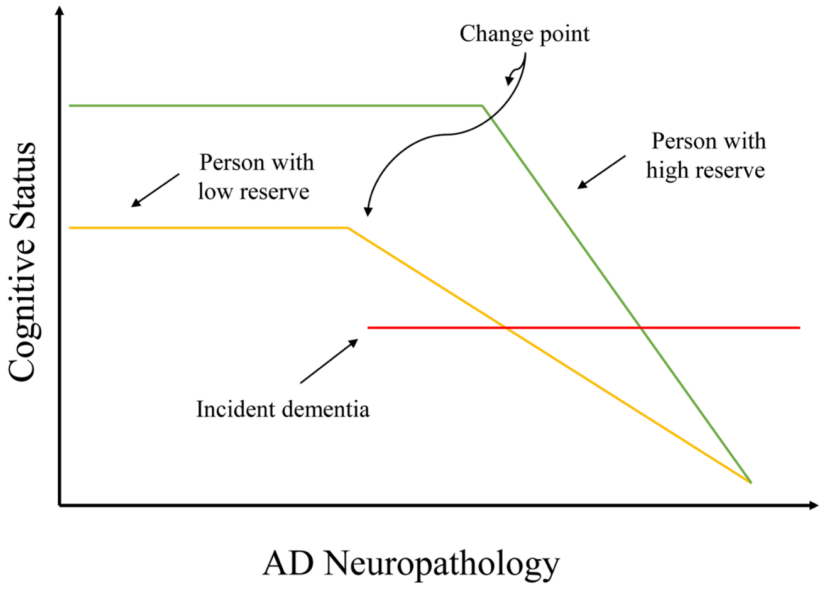

Figura 4. Representação do conceito de reserva cognitiva. A linha verde representa indivíduos com alta reserva cognitiva, a linha amarela representa indivíduos com baixa reserva e a linha vermelha o processo demencial. Indivíduos com alta reserva teriam capacidade de postergar os sintomas, pois é necessário maior aporte de patologia para deteriorar suas redes neurais. Fonte: (BARULLI; STERN, 2013).

Complementário às reservas, o modelo de Manutenção Cerebral foi desenvolvido por Nyberg e foi associado inicialmente ao envelhecimento cognitivo bem-sucedido (NYBERG et al., 2012). Ao invés de explicar os meios que alguns indivíduos lidam com o processo

patológico, o modelo de Manutenção determina que fatores – genéticos ou adquiridos por experiências de vida – protegem contra alterações patológicas ou relacionadas a idade. Alguns indivíduos adquirem resistência e sofrem menos com esses processos patológicos, o que determina uma maior capacidade cognitiva, provavelmente por estratégias de neuroplasticidade adjacentes (HABECK et al., 2016). Nesse contexto, ainda se questiona o mecanismo cerebral que determina o alto desempenho na senescência (CABEZA et al., 2018). Um modelo operacional proposto para o estudo do envelhecimento cognitivo bem-sucedido é através de idosos com alta capacidade cognitiva para a idade - ou Superidosos.

1.3 OS SUPERIDOSOS

No extremo oposto da demência no *continuum* cognitivo, um grupo de indivíduos parece não se adequar à via determinística do envelhecimento cognitivo. Inicialmente definidos por Mesulam *et al.* (HARRISON et al., 2012), esses indivíduos apresentam idade maior ou igual a 80 anos, mas memória semelhante a indivíduos de 20 a 30 anos mais jovem (GEFEN et al., 2014; HARRISON et al., 2012), sendo as outras funções normais para a idade.

O escore de memória episódica semelhante a indivíduos em meia-idade é o grande fator diferencial desse grupo. A memória declarativa episódica evidencia declínio típico relacionado ao envelhecimento normal entre os 60 – 65 anos (NYBERG et al., 2012). A determinação da idade igual a maior de 80 seleciona o grupo que não teve essa perda funcional. Além disso, a definição de Superidosos determina que outras funções sejam normais para a idade como a atenção, nomeação e fluência semântica (HARRISON et al., 2012).

Devido à grande variabilidade de estudos em relação a idosos com cognição acima da média, poucos dados se adequam à definição proposta de Superidosos. Dentre os poucos que seguem a definição, os testes de memória auditivo-verbal são os mais aplicados, especialmente o teste de aprendizagem auditório-verbal de Rey (do inglês Rey Auditory-Verbal Learning Test - RAVLT) (DEKHTYAR et al., 2017; GEFEN et al., 2014; HARRISON et al., 2012; JANECZEK et al., 2017; ROGALSKI et al., 2013). O grupo Superidosos, quando avaliado após 18 meses, demonstrou escore do RAVLT semelhante à primeira avaliação, ou seja, similar a indivíduos entre 50 e 60 anos (GEFEN et al., 2014). Dekhtyar *et al.* (2017) avaliou um grupo de idosos semelhantes ao descrito (75 anos ou mais com escore de memória acima de 80% do esperado) com 3 anos de diferença, mostrando que alto escore de memória não necessariamente implica em manutenção da capacidade cognitiva (Fig. 5) (DEKHTYAR et al., 2017). Questiona-se, portanto, se a alta capacidade de memória desse grupo seria atribuída à habilidade mnésica

prévia muito elevada (mas com decréscimo normal) ou se esse grupo simplesmente mantém as funções cognitivas na senescência (ROGALSKI et al., 2013).

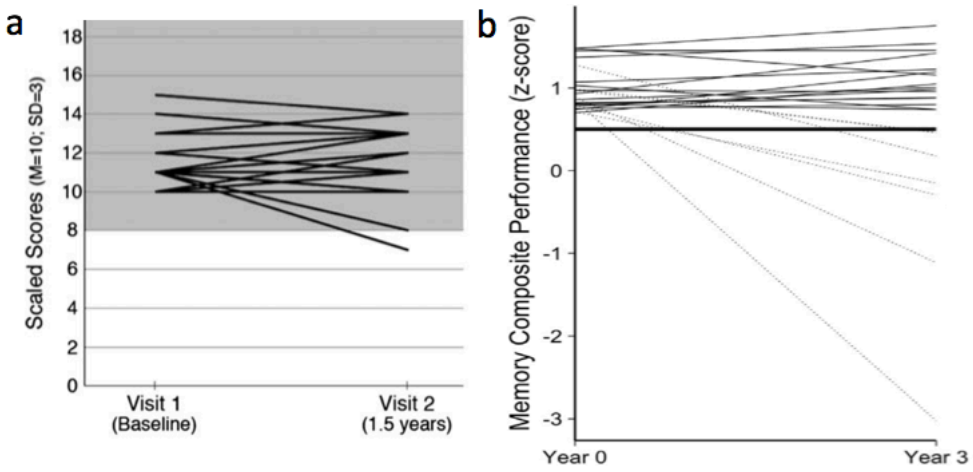

Figura 5. Avaliação longitudinal de memória em idosos com alta capacidade cognitiva. **a**. Escore de memória de 18 Superidosos, dos quais apenas 2 apresentaram declínio após 1,5 anos. **b**. Escore de memória de 25 indivíduos, dos quais 7 apresentaram declínio após 3 anos. Fonte: adaptado de (DEKHTYAR et al., 2017; GEFEN et al., 2014).

Os Superidosos foram estudados através de diversos métodos. Os exames de neuroimagem elevaram o estudo de cognição humana a outro patamar, permitindo técnicas de mapeamento cerebral de grandes estruturas corticais até nanomoléculas. Dentre os métodos realizados para análise cerebral desse grupo, destacam-se o uso do exame de Ressonância Magnética (RM) e de Tomografia por Emissão de Pósitrons com Tomografia Computadorizada (PET/CT). Invariavelmente, a mensuração de marcadores objetivos para quantificar medidas fisiológicas, como os descritos nesse tópico, é cada vez mais necessária. Seja pelos métodos de neuroimagem, seja por análise bioquímica, o estudo de biomarcadores é consagrado mundialmente e possui alta perspectiva de uso clínico. Atualmente, a DA é uma doença com características neuropatológicas únicas, medidas apenas através de biomarcadores de imagem multimodais (MÁRQUEZ; YASSA, 2019).

1.4 A NEUROIMAGEM

Atualmente, os métodos de neuroimagem abrangem desde alterações moleculares intracelulares até macroestruturais no cérebro *in vivo*. O exame de RM e de PET/CT são particularmente úteis no envelhecimento cognitivo e nas patologias neurodegenerativas. A RM funciona por emissão de energia do núcleo celular na mudança de campo magnético e gradiente de campo, fornecendo dados estruturais e funcionais (PLEWES; KUCHARCZYK, 2012). O PET/CT fornece imagens funcionais de processos moleculares no corpo através de

radioisótopos injetados no indivíduo (TER-POGOSSIAN et al., 1975). A utilização de neuroimagem tem sido cada vez maior, dada sua única capacidade de mensurar processos biológicos in vivo. Os próximos tópicos abrangem os aspectos técnicos e as alterações no *continuum* cognitivo característicos de RM e de PET/CT, respectivamente.

1.4.1 Ressonância Magnética

A RM mudou paradigmas na detecção de alterações cerebrais não mensuráveis com métodos clínicos. Essa técnica de imagem médica usa o princípio de ondas de radiofrequência geradas pelos núcleos atômicos submetidos a um forte campo magnético para obtenção de imagens de tecidos e órgãos internos (HUETTEL; SONG; MCCARTHY, 2014; KNIGHT et al., 2016). Atualmente, a RM é um método não apenas difundido para diagnóstico de várias patologias como também altamente confiável para uso em pesquisa. Softwares de processamento e análise fornecem dados precisos para análise volumétrica minuciosa de regiões específicas (FRISONI et al., 1996; REUTER et al., 2012).

Inicialmente projetada para análise anatômica de tecidos, a RM também permite quantificar processos fisiológicos através da RM funcional (RMf). A função cerebral emerge de interações sincrônicas entre áreas corticais, em relação temporal. A atividade neuronal é estimada através da técnica BOLD (do inglês *Blood-oxygen-level dependent signal),* que mensura a captação de oxigênio pelos neurônios pela mudança de oxigenação da hemoglobina (BISWAL et al., 1995; HUETTEL; SONG; MCCARTHY, 2014). As alterações na resposta BOLD permitem quantificar a função de resposta hemodinâmica (AZEEZ; BISWAL, 2017) em situações direcionadas (tarefas) ou situações em repouso. As conexões interregionais mostram-se ativas mesmo em estado de repouso, quando a rede cerebral padrão (rede *default)* mostra-se intensamente ativa (RAICHLE et al., 2001; SHEN, 2015). Essa rede é definida por atividade cerebral na ausência de tarefa específica e parece estar subjacente aos processos da consciência (BOLY et al., 2008) e de outras funções cognitivas, como memória e funções executivas (GREICIUS et al., 2004; SORG et al., 2007; WU et al., 2014).

Outro método estrutural da RM é chamado de Imagem por Tensores de Difusão (do inglês *Diffusion Tensor Imaging*, ou DTI) (BASSER; MATTIELLO; LEBIHAN, 1994). Essa sequência permite mensurar a difusão de moléculas de água em volume cerebral e, assim, identificar os tratos ou vias neurais (LE BIHAN, 1995). A mobilidade da molécula de água nos tecidos tende a ser altamente anisotrópica, ou seja, sem direção específica, mas nos axônios a anisotropia tende a ser menor. É medida, portanto, a anisotropia fracional (FA) e a difusividade

média (DM) de substância branca para estimar sua integridade (LE BIHAN et al., 2001; SULLIVAN; PFEFFERBAUM, 2006).

1.4.2 RM do *continuum* cognitivo

A RM tem papel fundamental em diferenciar certas mudanças estruturais decorrentes do envelhecimento fisiológico do patológico. A substância cinzenta apresenta perda volumétrica diferente em cada região cerebral, particularmente mais intensa até os 60 anos (SOWELL et al., 2003). A perda de volume decorrente do envelhecimento ocorre principalmente em regiões frontais (opérculo, giro pré-central, entre outras), giro parietal superior, insula, cingulado anterior (GOOD et al., 2001; SALAT, 2004). No entanto, algumas áreas mesiais demonstram relativa preservação com o envelhecimento, como tálamo, amigdala, hipocampos e córtex entorrinal bilateralmente (JERNIGAN et al., 1991; SALAT, 2004). Contrastando o envelhecimento normal, algumas regiões apresentam alta taxa de atrofia na DA: hipocampos, córtex entorrinal, neocortex temporal (CHETELAT; BARON, 2003; DUBOIS et al., 2014; VAN DE POL et al., 2006).

A rede default também demonstra alteração relacionada à senescência. Áreas mais anteriores da rede default, relacionadas com atenção, velocidade de processamento e função executiva, são mais vulneráveis à perda de conectividade funcional com o envelhecimento: giro frontal superior e médio, cingulado posterior, giro temporal médio e parietal superior bilateralmente (ANDREWS-HANNA et al., 2007; DAMOISEAUX et al., 2008). Um estudo longitudinal mostra que idosos saudáveis falham em desativar essa rede (PERSSON et al., 2014). Estágios iniciais e demenciais da DA apresentam disfunção generalizada da rede default, principalmente entre hipocampo/córtex entorrinal e o córtex cingulado posterior (CHA et al., 2013; GREICIUS et al., 2004).

Estudos de difusão na RM demonstram um padrão específico do envelhecimento. De maneira global, ocorre aumento de DM e diminuição generalizada de FA (KNIGHT et al., 2016; SULLIVAN; PFEFFERBAUM, 2006). Idosos apresentam diminuição de conexões pré-frontais, corpo caloso e cápsula interna, enquanto conexões temporais e posteriores são relativamente preservadas (SALAT et al., 2005). Estágios avançados da DA possuem achados de DTI compatíveis com diminuição de FA em todas regiões, marcadamente menor no fascículo uncinado, fascículo lateral superior e corpo caloso (SEXTON et al., 2011). Alterações da DTI em Comprometimento Cognitivo Leve (CCL) amnéstico, entidade clínica pré-demencial da DA, são mais robustas em tratos que passam pelo lobo temporal e regiões posteriores do cérebro (NIR et al., 2013).

Indivíduos definidos como Superidosos apresentaram características únicas em RM estrutural. Esses idosos sofrem menos atrofia cortical e demonstram o cíngulo anterior mais espesso que idosos normais e até mesmo maior que indivíduos de meia-idade (Fig. 6) (COOK et al., 2017; HARRISON et al., 2012, 2018). Uma análise longitudinal desse grupo demonstrou que Superidosos tem menor atrofia cortical global que controles após 18 meses (COOK et al., 2017). No entanto, outro estudo mostrou que idosos com alta capacidade cognitiva (apesar de não se adequar exatamente à definição de Superidosos) tiveram perda de volume hipocampal similar aos controles (DEKHTYAR et al., 2017).

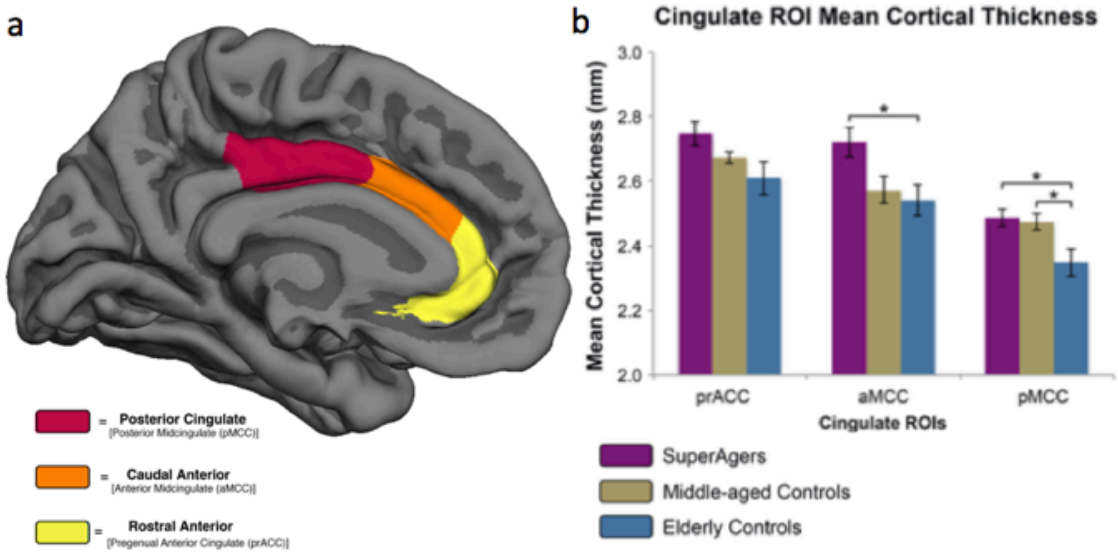

Figura 6. Espessura cortical do córtex cingulado de Superidosos. **a**. Divisão morfofuncional do giro cingulado em cingulado posterior (pMCC), cingulado caudal anterior (aMCC) e cingulado rostral anterior (prACC). **b**. Gráfico comparativo da espessura cortical de cada região do cíngulo nos três grupos do estudo: Superidosos, Controles de Meia-Idade e Controles Idosos. Adaptado de (GEFEN et al., 2015).

1.4.3 Tomografia por Emissão de Pósitrons

O uso da tomografia por emissão de pósitrons no mapeamento cerebral é bem consolidado atualmente (KRISHNAMOORTHY; SCHMALL; SURTI, 2017). Esse método apresenta inúmeras vantagens em relação a outros métodos não-invasivos, pois permite mensurar tanto processos metabólicos intracelulares quanto os próprios metabólitos específicos. Nesse contexto, alterações moleculares cerebrais parecem surgir muito antes de alterações estruturais e clínicas (DONOHUE et al., 2017; OSSENKOPPELE et al., 2015).

Neste estudo são usados dois radiofármacos associados a dois radioisótopos: a [^{18}F]Fluorodesoxiglicose (FDG) e o [^{11}C]*Pittsburgh Compound B (PIB)*. O estudo molecular de neurodegeneração através do PET/CT teve início com o metabolismo celular através do

radiofármaco FDG (FERRIS et al., 1980), molécula marcada com Fluor-18, que possui meia-vida de 110 minutos após sua produção. Como o consumo de glicose pelo neurônio é diretamente relacionado a sua atividade neuronal (SOKOLOFF et al., 1977), o FDG é usado como marcador de disfunção sináptica e lesão neuronal (ROCHER et al., 2003). Para isso, algumas medidas são tomadas na realização do exame, a fim de evitar erro na análise do exame. São exemplos dessas medidas: (1) a mensuração da glicemia logo antes da aquisição das imagens, sendo necessário estar entre 70 – 120 mg/dL e (2) o repouso por pelo menos 30 minutos antes da aquisição das imagens, evitando atividade cerebral específica (KRISHNAMOORTHY; SCHMALL; SURTI, 2017).

Atualmente, a deposição amiloide cerebral caracteristicamente associada à DA é comprovada pelo PET/CT através do radiofármaco PIB (KLUNK et al., 2004). Com afinidade nanomolecular pela forma fibrilar insolúvel da βA (JOHNSON, 2006), este radiofármaco é o marcador com maior validade e mais extensamente usado em pesquisas sobre a DA, contando com alta sensibilidade e especificidade para a patologia (KLUNK et al., 2004; NOBLE; SCARMEAS, 2009; OSSENKOPPELE et al., 2015). Derivado da tioflavina marcada com Carbono-11, o PIB possui uma meia-vida de 20 minutos e tem seu uso restrito a centros com produção do seu composto. Klunk e colegas (KLUNK et al., 2004) demostraram que o padrão de distribuição do PIB no PET em pacientes com DA é muito consistente com o padrão de deposição amiloide em estudos *post-mortem*, provando a alta sensibilidade deste composto no diagnóstico. Nem todos pacientes são candidatos à imagem com amiloide. Os critérios para solicitação de imagem amiloide são: (1) pacientes com CCL persistente ou progressivo e inexplicado, (2) pacientes com critérios-chave para DA possível que incluem apresentações atípicas ou etiologicamente mistas, e (3) pacientes com demência de início atipicamente precoce (JOHNSON et al., 2013).

Além do PIB, outros radiotraçadores da placa βA estão em desenvolvimento ou em fases de teste: [18F]NAV4694, [18F]Florbetapir, [18F]Florbetaben, [18F]Flumetemol (SCHILLING et al., 2014). A agência de regulação americana FDA aprova o uso clínico de florbetapir, flutemetamol e florbetaben.

1.4.4 PET do *continuum* cognitivo

O envelhecimento fisiológico é marcado por uma série de mudanças anatômicas e funcionais, dentre elas a captação de FDG. Idosos com declínio cognitivo esperado para a idade apresentam hipometabolismo particularmente acentuado em áreas do lobo frontal, mas também em córtex cingulado anterior e córtex orbitofrontal bilateralmente (MOELLER et al., 1996;

PARDO et al., 2007; ZUENDORF et al., 2003) (Quadro 1). Algumas regiões apresentam pouco ou quase nenhuma perda metabólica com esse processo, principalmente subcorticais: córtex motor primário, precúneo, áreas do lobo temporal mesial, entre outras (GRIEVE et al., 2005; KALPOUZOS et al., 2009). A captação de FDG em estágio demencial da DA possui padrão específico e diferente de outras condições clínico-patológicas: hipocaptação em precúneo, córtex temporparietal e cingulado posterior são as áreas mais afetadas nesse estágio da doença (Fig. 7) (MOSCONI et al., 2008a).

Hipometabolismo	**Metabolismo mantido**
Lobo frontal: • Córtex cingulado anterior • Córtex pré-frontal medial e dorsolateral • Córtex orbitofrontal Insula Lobo temporal: • Polo temporal • Córtex temporal lateral Lobo parietal: • Córtex parietal inferior, superior e supramarginal	Cortex motor primário Lobo occipital: • Áreas visuais • Córtex cingulado posterior Precúneo Lobo temporal mesial: • Hipocampo • Amígdala • Giro parahipocampal Tálamo Putamen e globo pálido Cerebelo

Quadro 1. Metabolismo regional associado ao envelhecimento. Fonte: Adaptado de Berti (BERTI; MOSCONI; PUPI, 2014).

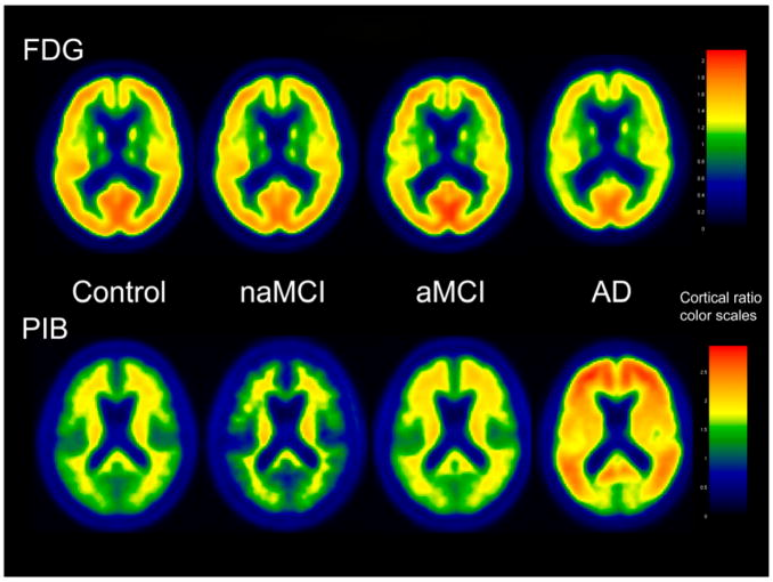

Figura 7. Média de captação de FDG e PIB em indivíduos com diferentes progressões da DA e com naMCI. Regiões com maior captação em vermelho e amarelo. naMCI: *non-amnestic mild cognitive impairment;* aMCI: *amnestic mild cognitive impairment*; AD: *Alzheimer's disease.* Fonte: (MOSCONI et al., 2008b).

Atualmente, questiona-se até que ponto o acúmulo de placa amiloide cerebral é parte do envelhecimento (VILLAIN et al., 2012). Estudos apontam para maior captação de PIB em indivíduos com DA estágio demencial e até mesmo fases pré-clínicas, principalmente em precúneo, cíngulo posterior, córtex frontal e núcleo caudado (EDISON et al., 2007; ROWE et al., 2007). A positividade para o marcador amiloide indica maior chance de declínio cognitivo em pessoas assintomáticas, e seu aumento gradual também sinaliza para prejuízo cognitivo futuro (INSEL et al., 2016; JANSEN et al., 2015). Recentemente, uma nova definição de DA foi proposta para o uso em pesquisa, a qual envolve o uso de biomarcadores (JACK et al., 2018), denominada AT(N). A letra **A** corresponde ao depósito amiloide, mensurável por PET-PIB (ou outro marcador PET-amiloide) ou líquor; a letra **T** corresponde ao marcador de tau-p, através de PET-Tau ou líquor; a letra **(N)** corresponde a neurodegeneração, mensurável por PET-FDG, RM ou líquor (tau total) (Tabela 1). Para o diagnóstico (no contexto da pesquisa), é necessário o marcador A+ e T+, havendo ou não (N). Importantemente, a coleta de dados descrita no decorrer desta tese foi realizada antes desta definição e, portanto, foram aplicados os critérios diagnósticos precedentes (IWG-2) (DUBOIS et al., 2014).

<table>
<tr><th>AT(N) profiles</th><th colspan="2">Biomarker category</th></tr>
<tr><td>A-T-(N)-</td><td colspan="2">Normal AD biomarkers</td></tr>
<tr><td>A+T-(N)-</td><td>Alzheimer's pathologic change</td><td rowspan="4">Alzheimer's continuum</td></tr>
<tr><td>A+T+(N)-</td><td>Alzheimer's disease</td></tr>
<tr><td>A+T+(N)+</td><td>Alzheimer's disease</td></tr>
<tr><td>A+T-(N)+</td><td>Alzheimer's and concomitant suspected non Alzheimer's pathologic change</td></tr>
<tr><td>A-T+(N)-</td><td colspan="2">Non-AD pathologic change</td></tr>
<tr><td>A-T-(N)+</td><td colspan="2">Non-AD pathologic change</td></tr>
<tr><td>A-T+(N)+</td><td colspan="2">Non-AD pathologic change</td></tr>
</table>

Tabela 1. Perfis AT(N) e categorias diagnósticas de acordo com os biomarcadores. A presença de A+ indica que o participante está no *continuum* da DA, mesmo não apresentando T+ ou (N)+. Fonte: (JACK et al., 2018).

Um recente estudo longitudinal avaliou a deposição amiloide em idosos com alta capacidade cognitiva, mas sem usar a definição de Superidosos (DEKHTYAR et al., 2017).

Esses idosos tem memória semelhante, mas idade menor que a definição de Superidosos. Foi demonstrado que idosos com alta capacidade de memória podem ser subdivididos em 2 subgrupos: os que mantém e os que diminuem o escore de memória após 3 anos. O depósito amiloide é significativamente menor no subgrupo de idosos que manteve a alta performance de memória após 3 anos em comparação com o outro grupo. Além disso, o grupo que manteve alta performance apresentou acúmulo mais lento de placas. Harrison et al. (2018) também demonstrou similar depósito amiloide entre idosos de alta performance e idosos normais para a idade, porém revelou menor carga amiloide entre idosos de alta performance com idade mais avançada (HARRISON et al., 2018).

2 JUSTIFICATIVA DO ESTUDO

A gerontologia ainda não contempla consistentemente a definição de envelhecimento cerebral fisiológico ou patológico, principalmente em questões clínicas. Algumas alterações de neuroimagem são evidentes e contrastam com as patologias neurodegenerativas, porém ainda resta correlacionar os dados para definição deste estágio da vida.

Os mecanismos fisiopatológicos da DA permanecem incertos, apesar do esforço mundial. As regiões com depósito de placa amiloide estão relacionadas com as áreas de hipometabolismo, fortalecendo a evidência de morte neuronal. A conectividade cerebral é posteriormente afetada, gerando prejuízos clínicos e queda da qualidade de vida do indivíduo. Por fim, atrofia neocortical e perda de substância branca exibem tardiamente o efeito deletério da morte neuronal e dano cerebral.

Pela primeira vez se estuda de maneira multimodal o funcionamento cerebral de indivíduos longevos com alta performance cognitiva. Este trabalho propõe-se a avaliar as funções cognitivas em associação com metabolismo de glicose cerebral, depósito amiloide, conectividade funcional e conectividade estrutural desses indivíduos.

Portanto, o estudo de Superidosos se justifica pela busca de biomarcadores de alta performance cognitiva em longevos. Sustentado pelo aumento alarmante de casos de DA no mundo, com estratégias de prevenção insuficientes e tratamento ainda mais frustrantes, o estudo do envelhecimento saudável tem papel fundamental. Esses biomarcadores são potenciais alvos terapêuticos em estudos intervencionais para melhora cognitiva na longevidade, com impacto direto em uma parcela crescente da população. Além disso, este estudo busca integrar multimodalidades na busca desses marcadores, o que aumenta a probabilidade de sucesso. Justifica-se então a busca de uma assinatura metabólica, estrutural e funcional em Superidosos para estudo de novas estratégias de diagnóstico precoce e de alvos terapêuticos, com impacto importante na saúde pública e na mudança de paradigmas sobre envelhecimento normal e patológico.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Analisar o padrão de deposição amiloide, metabolismo de glicose, estrutura cortical, conectividade funcional e padrão de difusividade cerebral de idosos com cognição elevada (Superidosos, *SuperAgers* ou SA) para a idade em relação aos grupos Controles de meia-idade (C50) e Controles de 80 anos (C80).

3.2 OBJETIVOS ESPECÍFICOS

Avaliar:

1. Diferença de depósito amiloide regional e global entre os grupos SA vs. C80 e SA vs. C50, através do radiofármaco PIB.
2. Diferença de metabolismo cortical regional e global entre os grupos SA vs. C80 e SA vs. C50, através do radiofármaco FDG.
3. A conectividade funcional relacionada aos grupos SA vs. C80 e SA vs. C50, através da RMf.
4. A espessura cortical de determinadas regiões do grupo SA em comparação com os grupos C80 e C50.
5. A volumetria de determinadas regiões do grupo SA em comparação com os grupos C80 e C50.

PARTE II

4 MÉTODOS

4.1 DELINEAMENTO

Estudo clínico transversal observacional.

4.2 IMPLEMENTAÇÃO DO ESTUDO

Indivíduos indicados ou que se voluntariaram ao estudo foram submetidos ao protocolo desta pesquisa, dividido em 3 partes. A etapa 1 consistiu em entrevista telefônica com aplicação do questionário de Pre-Screening (Anexo C) para análise de critérios de exclusão e breve explicação do estudo. Os indivíduos sem critérios de exclusão foram avaliados no Instituto do Cérebro do Rio Grande do Sul, na etapa 2, com avaliação clínica (Screening - Anexo D), simulação de RM, testagem neuropsicológica e posterior classificação em grupos. Indivíduos com critérios de inclusão para um dos 4 grupos foram submetidos à etapa 3, com realização dos exames de imagem: RM, PET/CT marcado com FDG e PET/CT marcado com PIB, em dois dias (Fig. 8).

O Consentimento Livre e Esclarecido foi obtido para uso dos dados clínicos (Anexo B). O presente estudo foi aprovado no Comitê de Ética em Pesquisa desta instituição sob parecer número 1.608.823 (Anexo A).

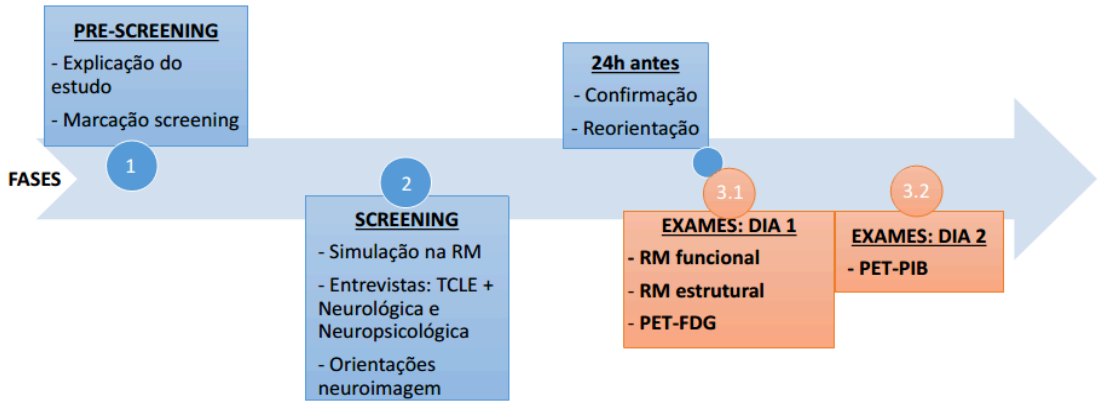

Figura 8. Fluxograma de participantes da pesquisa.

4.3 POPULAÇÃO ALVO

Indivíduos provenientes de consultórios, dos ambulatórios do Serviço de Neurologia do Hospital São Lucas da PUCRS, do Centro de Extensão Universitária Vila Fátima da PUCRS e da própria sociedade.

4.4 CRITÉRIOS DE INCLUSÃO

1. Idade maior que 50 anos;
2. Alfabetizado;
3. Assinatura do Termo de Consentimento Livre e Esclarecido (TCLE, Anexo B);

4.5 CRITÉRIOS DE EXCLUSÃO

1. Impossibilidade de obter acesso vascular para injeção percutânea;
2. Portadores de neoplasias malignas;
3. Portadores de doenças auto-imunes;
4. Portadores de outras doenças neurológicas ou psiquiátricas;
5. Portadores de doença vascular cerebral (FAZEKAS>2, insultos isquêmicos corticais agudos ou prévios) (FAZEKAS et al., 1987);
6. Portadores de insuficiência cardíaca aguda ou descompensada;
7. Portadores de doenças hematológicas primárias;
8. Insuficiência hepática;
9. Insuficiência renal moderada;
10. Gestantes;
11. Participação de outro ensaio clínico;
12. Presença de prótese metálica ou objeto ferromagnético fixo no corpo.

4.6 DESCRIÇÃO GERAL DO ESTUDO

4.6.1 Perfil neuropsicológico

Os indivíduos que aceitaram a participação no estudo e assinaram o TCLE foram submetidos a uma bateria de testes neuropsicológicos (Anexo F). Os testes neuropsicológicos foram escolhidos com base em estudos relevantes sobre cognição em idosos e diagnóstico precoce de DA (HARRISON et al., 2012; MORRIS et al., 1989) (Tab. 2).

Teste	Função avaliada	Validação
ACE-R	Cognição global	Carvalho
MoCA	Rastreio de declínio cognitivo	Cecato
RAVLT	Aprendizagem auditivo-verbal Memória curto-prazo Memória episódica	Malloy-Diniz
TMT (A e B)	Atenção Memória de trabalho Flexibilidade mental Velocidade de processamento visual	Campanholo
BNT	Nomeação	Miotto
CFT	Fluência semântica	Brucki
F A S	Fluência fonológica	Machado
Digit Span	Memória de trabalho Memória de curto-prazo	Zimmermann
FAQ	Funcionalidade Autonomia	Dutra
GDS-15	Sintomas depressivos	Paradela

Tabela 2. Domínios cognitivos avaliados por teste neuropsicológico.

Nessa avaliação foram utilizados testes clínicos de avaliação cognitiva geral, como o *Addenbrooke's Cognition Evaluation - Revised* (ACE-R) (AMARAL-CARVALHO; CARAMELLI, 2012; CARVALHO; CARAMELLI, 2007) e o *Montreal Cognitive Assessment* (MoCA, Anexo E) (CECATO et al., 2014) e testes específicos para cada domínio cognitivo (Tabela 1). A aprendizagem auditivo-verbal e memória episódica tardia foi avaliada através do *Rey Auditory-Verbal Learning Test* (RAVLT) (IVNIK et al., 1999; MALLOY-DINIZ et al., 2007); a memória de trabalho e atenção, através do *Trail Making Test* – A e B (CAMPANHOLO et al., 2014; MORRIS et al., 1989; RANDOLPH et al., 1998) e do *Digit Span* (DS) – ordem direta e inversa (WECHSLER, 1939; ZIMMERMANN et al., 2015); a linguagem, através do *60-item Boston Naming Test* (BNT) (KAPLAN; GOODGLASS; WEINTRAUB, 1983; MIOTTO et al., 2010); a fluência verbal, através do *Category Fluency Test* – Animais (CFT)(BRUCKI et al., 1997) e do FAS (MACHADO et al., 2009) (Tab. 2).

O teste ACE-R se propõe a avaliar diversas funções cognitivas de maneira segmentada, incluindo o Mini-Exame do Estado Mental (MEEM) como subescore final. O MoCA é um teste de rastreio cognitivo com alta sensibilidade e especificidade para declínio cognitivo, usado rotineiramente na avaliação neurológica de indivíduos com queixas de memória. No RAVLT, quinze palavras foram lidas aos participantes, as quais devem ser memorizadas e evocadas 20 minutos após, pontuando o número de palavras evocadas na aprendizagem, após uma lista distratora. No TMT, o indivíduo precisa manter na memória de trabalho a sequência lógica da tarefa e conectar números sequenciais – alternando com letras no caso TMT-B. O BNT é usado para avaliar a nomeação de diversas figuras. No CFT, o participante deve dizer o maior número de palavras com relação semântica em um período de limitado tempo. No DS, o indivíduo deve usar a memória de trabalho para enumerar a maior sequência de dígitos, em ordem normal ou em ordem inversa àquela verbalizada pelo avaliador. Todos os testes foram pontuados de acordo com valores normatizados e validados para amostras brasileiras, de acordo com idade e escolaridade.

Como parte integrante da testagem, foi realizado o *Functional Assessment Questionnaire* (FAQ) de Pfeffer (DUTRA et al., 2015; PFEFFER et al., 1982) e a Escala de Depressão Geriátrica de 15 itens (*Geriatric Depression Scale*, GDS-15) (PARADELA; LOURENÇO; VERAS, 2005). Apesar de não mensurarem uma função cognitiva, esses testes são essenciais para evitar fatores de confusão, no caso, perda de funcionalidade e sintomas depressivos.

4.6.2 Seleção de Indivíduos

Inicialmente, indivíduos provenientes da sociedade foram avaliados para os critérios de exclusão por telefone. Indivíduos não-excluídos foram avaliados para critérios de inclusão com anamnese detalhada e exame físico, seguido da testagem neuropsicológica. Indivíduos que preencheram os critérios foram classificados em 4 grupos: (I) Superidosos, (II) Controle - 50 anos, (III) Controle – 80 anos e (IV) Doença de Alzheimer, estágio demencial leve.

O grupo em estudo, Superidosos, foi comparado a dois grupos controles: o controle cognitivo (Controle - 50 anos, ou C50), e o controle de idade (Controle – 80 anos, ou C80). Além disso, foi feita comparação com grupo patológico (Doença de Alzheimer, ou DA). A seleção dos grupos foi feita a partir de estudo prévio (HARRISON et al., 2012), conforme critérios a seguir:

I. **Superidosos (SI)**: idade maior ou igual a 80 anos, com escore da lista A7 do RAVLT maior ou igual à média de indivíduos de 50 a 60 anos (escore bruto ≥ 10). Os testes TMT-B, BNT e FAS devem ter escore dentro ou acima de um desvio-padrão da média para idade, de acordo com valores tabelados para idade e escolaridade de cada teste.

II. **Controles Meia-idade (C50)**: idade entre 50 a 65 anos, com os testes RAVLT-A7, TMT-B, BNT e FAS dentro de 1 desvio-padrão para média da idade.

III. **Controles Idosos (C80)**: idade maior ou igual a 80 anos, testes RAVLT-A7, TMT-B, BNT e FAS dentro de 1 desvio-padrão para média da idade.

IV. **Doença de Alzheimer (DA)**: idade maior ou igual a 80 anos que preenchem critério clínico para Doença de Alzheimer (DA) típica, estágio demencial leve (DUBOIS et al., 2014). O diagnóstico de DA exige história progressiva de prejuízo amnéstico de domínio hipocampal com algum biomarcador positivo (Quadro 2). Os testes neuropsicológicos não são determinantes neste grupo, servindo para fins comparativos. Esse grupo foi selecionado para critérios de comparação dos métodos utilizados, mas seus resultados não serão discutidos.

A – Fenótipo clínico específico: presença de um **episódio prévio** e significante de prejuízo de memória (isolado ou associado com outra mudança comportamental ou cognitiva que sugere CCL ou síndrome demencial) com as características: • Mudança gradual e progressiva na **memória**, avaliado pelo paciente ou um informante a mais de 6 meses; • Evidência objetiva de **síndrome amnésica** tipo hipocampal, com base em prejuízo funcional significante em teste de memória episódica com especificidade para DA, p.e. recordação com pistas em testes de aquisição de memória.	B – Evidência in-vivo de patologia da doença de alzheimer (necessário 1)**:** • Diminuição de $\beta a_{1\text{-}42}$ com aumento de tau-t ou tau-p no exame de líquor; • Aumento da retenção de marcador amiloide na PET; • Presença de mutação dominante autossômica em PSEN1, PSEN2 ou APP.

Quadro 2. Critérios diagnósticos para Doença de Alzheimer típica, segundo IWG-2. São necessários critérios A mais um critério B. Fonte: (DUBOIS et al., 2014).

4.6.3 RM: aquisição e processamento de imagens

4.6.3.1 Aquisição de imagens de RM

As imagens de ressonância magnética foram adquiridas em uma ressonância de 3 Tesla do modelo GE Signa HDxT utilizando bobina de 8 canais. O protocolo foi baseado em protocolo internacional definido pelo estudo multicêntrico Alzheimer's Disease Neuroimaging Initiative (ADNI) (INITIATIVE, 2015).

Foram realizados os seguintes protocolos de imagem durante o exame:

- Imagens ponderada em **T1** (sequência 3D; TE=2256ms; Flip Angle = 11; Tamanho Matriz = 256x256; FOV = 512x512mm; Espessura de corte= 1mm; Gap entre cortes= 1mm);
- Imagens **FLAIR** (TR=11002ms; TE=150,12ms; Tamanho Matriz =384x320; FOV=512x512mm; Espessura de corte= 5mm; Gap entre cortes=5,5mm; Flip Angle=90);
- Imagens ponderadas em **T2** (TR=4333,34; TE=133,28ms; TI=0ms; Tamanho Matriz = 512x256; FOV = 512x512mm; Espessura de corte= 5mm; Gap entre cortes=5,5mm, Flip angle=90);
- Imagens ponderadas por **tensores de difusão** (**DTI**) (TR=13s; TE=82,4ms; Tamanho Matriz=128x128; FOV=256x256mm; Espessura de corte=2,5mm; Gap entre cortes=0mm, número de direções=33, número de imagens T2=50, b-value=750, Frames=1700);
- Ressonância magnética **funcional** no estado de repouso (Echo-Planar Imaging, TR=2000ms; TE=30ms; TI=0; Tamanho Matriz=64x64; FOV=64x64mm; Espessura de corte= 3.6; Gap entre cortes=3,9; Frames=6090; número de volumes=205; Flip Angle =90); Tempo total da sequência funcional: 7 minutos.

Antes de iniciar a sequência funcional, o participante foi instruído a "não pensar em nada" com objetivo de não manter o pensamento fixo em um conceito ou em uma memória específica. Durante a aquisição, foi realizada a mensuração em tempo real de movimentos da cabeça acima do limite (movimentos ≥ 3mm por slice). Participantes que tiveram 15 ou mais movimentos acima do limite repetiram a sequência funcional. O tempo total de exame foi em torno de 40 minutos por participante.

4.6.3.2 Processamento e análise de imagens de RMf

Todas sequências de RM (dados no formato DICOM), incluindo a sequência funcional, foram coletadas diretamente da máquina, transferidas para três bancos de dados (XNAT,

LABIMA e HD Externo) e então organizadas em formato DICOM. O processamento funcional envolve corregistro com a sequência estrutural (FSPGR BRAVO, T1 volumétrica), a qual também foi coletada e organizada de acordo.

As imagens foram primeiramente transformadas em formato NIFTI com o software dcm2nii (LI et al., 2016). Após, foram realizadas as etapas de pré-processamento através do programa AFNI (*Analysis of Functional Neuroimaging, https://afni.nimh.nih.gov*), script afni_proc.py compreendendo os seguintes passos: Despiking, correção do tempo dos cortes e de movimento, alinhamento da imagem funcional com a estrutural, registro para o espaço padrão (MNI152), borramento usando um kernel fwhm de 6mm, escalonamento (média de zero de desvio padrão igual a 1 para a linha de tempo), aplicar uma mascara binária do cérebro, aplicação de regressores de ruído (6 parâmetros de movimento e sinal médio da substância branca e fluído cerebroespinhal). Controle de qualidade foi feito para cada etapa, sendo necessária a correção manual da segmentação quando não se obteve corregistro adequado.

Foram calculadas três medidas de conectividade funcional neste estudo: *Regional Homogeneity* (ReHo) (JIANG; ZUO, 2016), *Seed-based Correlation analysis* e *Independent Component Analysis* (ICA). Também foi realizada uma medida de análise da frequência do sinal, *fractional Amplitude of Low-Frequency Fluctuations* (fALFF).

O cálculo de ReHo foi feito através do comando 3dReHo no AFNI (TAYLOR; SAAD, 2013), com cluster de 27 voxels, que calcula a correlação estatística de Kendall entre um voxel e seus 27 voxels adjacentes. Assim, essa análise permite avaliar a interconectividade local, dado que a variação do sinal de um voxel está temporalmente correlacionada com seus voxels adjacentes. É criado então um mapa cerebral com ativações de conectividades dos clusters para cada indivíduo. Os grupos foram comparados através de ANOVA através do comando 3dMVM (CHEN et al., 2014), comparando-se separadamente os pares de grupos (SA vs. C80, C80 vs. C50 e SA vs. C50).

A *seed-based correlation analysis* é uma das técnicas mais simples de análise de conectividade funcional. Seleciona-se uma região-de-interesse (ROI), e então a variação do sinal deste ROI é correlacionada com todos os outros voxels do cérebro, criando um mapa de conectividade para aquele ROI. Foram definidas 4 ROIs com base no atlas *Hammersmith* N30R83 (GOUSIAS et al., 2008; HAMMERS et al., 2003) em áreas previamente relacionadas à idosos com alta performance de memória (DONOHUE et al., 2017; HARRISON et al., 2012): cíngulo anterior presubgenual, cíngulo anterior subgenual, cíngulo anterior e cíngulo posterior. Foi extraído o valor do *timeseries* do determinado ROI, então calculado o mapa de conectividade para cada indivíduo e posteriormente comparado entre os grupos com o comando

3dMVM, citado previamente. Também foi realizada análise de regressão multivariada através de *General Linear Model* (GLM) dos mapas de conectividade de cada ROI e os escores de recordação tardia de memória (lista A7 do RAVLT), ajustado para idade. Foi utilizado o comando 3dRegAna com os grupos SA, C50 e C80, e idade como cofator.

A *Independent Component Analysis* é um método para análise de mapas espaço-temporais estatisticamente independentes (CALHOUN; LIU; ADALI, 2009). Essa abordagem maximiza independência entre mapas de conectividade funcional, permitindo a identificação de diferentes redes neurais. Foi realizada ICA determinando 10 componentes independentes na amostra. Foram selecionados os componentes espaciais que envolviam áreas do córtex cingulado e hipocampais, além da rede Default Mode, Salience e Atenção Dorsal (FOX et al., 2005; RAICHLE et al., 2001). Após a identificação das redes, foi feita *dual regression* nos componentes selecionados para extração dos mapas com curso de tempo normalizados para cada indivíduo, permitindo análise estatística. Foi realizada comparação entre grupos com ANOVA através do comando 3dMVM e regressão linear múltipla, utilizando 3dRegAna com os escores de recordação tardia de memória (Lista A7 do RAVLT), usando a idade como cofator.

Além das análises de conectividade, também foi realizada a medida de amplitude de alteração do sinal, o fALFF. Essa técnica quantifica a amplitude de oscilações de baixa frequência do sinal BOLD em um limite de frequência (entre 0.1 – 0.01 Hz) e compara com o poder da oscilação em todas frequências detectáveis. O mapa resultante da medida de fALFF de cada participante foi usado para realizar comparação entre grupos através de ANOVA, pelo comando 3dMVM.

4.6.3.3 Processamento e análise de imagens de RMe

A reconstrução cortical e segmentação volumétrica foi realizada com o software FreeSurfer v6.0, que é documentado e gratuitamente disponível para download (http://surfer.nmr.mgh.harvard.edu/). Os detalhes técnicos foram descritos em publicações prévias (DALE; FISCHL; SERENO, 1999; DALE; SERENO, 1993; DESIKAN et al., 2006; FISCHL et al., 2002; FISCHL; DALE, 2000), incluindo uma série de procedimentos que diminuem o erro de segmentação e parcelamento subcortical e cortical, respectivamente. Esse método usa tanto a informação de intensidade quanto a de continuidade das 3 dimensões da imagem para produzir representação de espessura cortical, medida como menor distância entre substância branca/cinzenta até cinzenta/líquor em cada vórtice da superfície tecelada. O método foi validado para uso em pesquisa e comparado com estudos histológicos (ROSAS et al., 2002).

Os procedimentos realizados com cada volume cerebral compreenderam: utilização do comando recon-all, avaliação tridimensional para controle de qualidade e correção manual de erros provenientes da reconstrução. Os erros decorrentes da reconstrução são divididos em: erros de retirada do crânio, erros de segmentação, erros de normalização de intensidade, erro na delimitação pial e defeito topológico. Todos os erros foram corrigidos pela interface FreeView, incluída no FreeSurfer, utilizando pontos-de-controle ou deleção de áreas piais inapropriadamente incluídas (por exemplo, dura-máter considerada área pial). Os volumes cerebrais foram reavaliados novamente e o processo repetido até que houvesse mínimo prejuízo de segmentação e parcelamento do cérebro.

A análise estatística foi realizada através da interface QDEC para análise a nível de voxel, um *software* integrante do FreeSurfer. Análise de grupo foi realizada através de modelo geral linear (GLM) usando a interface QDEC, usando como cofator os escores de recordação tardia (Lista A7 do RAVLT).

4.6.4 PET/CT: aquisição e processamento de imagens

4.6.4.1 Aquisição de imagens de PET/CT

As imagens de PET/CT foram adquiridas em equipamento Discovery D600 (GE Healthcare). Este equipamento conta com cristais detectores do tipo BGO, capazes de adquirir 47 cortes com espessura de 3,27 mm (extensão axial de 15,4 cm). As imagens foram adquiridas em modo 3D com resolução intrínseca axial de 5,6 mm e transaxial de 5,1 mm, com campo transaxial de visão total de 70 cm. Também foi aplicada correção de atenuação de fótons. Ambos exames foram realizados sob condições padronizadas de repouso e sem estímulos audiovisuais. O participante teve a limitação dos movimentos da cabeça no *gantry* e foi orientado a não movimentá-la durante os procedimentos.

O exame de PET/CT foi realizado em um primeiro momento com a Fluorodesoxiglicose (FDG). Todos indivíduos estavam com glicemia capilar entre 70-120 mg/dL 10 minutos antes do momento do exame de FDG. Consecutivamente, o segundo exame de PET/CT foi realizado em outro dia, dentro de uma semana, com o *Pittsburgh Compound B* (PIB).

No primeiro dia, o participante foi orientado a seguir uma dieta pobre em hidrocarbonetos 24h antes da realização do procedimento, com objetivo de padronizar dieta e reduzir efeitos secundários à alimentação. O participante permaneceu repouso, em sala com mínima quantidade de estímulos auditivos e visuais, 30 minutos antes do exame. A aquisição foi realizada após a injeção endovenosa, “em bolus”, de FDG, na dose de 326 (± 47) mBq, em participantes que realizaram o preparo e o jejum de 4 horas. A aquisição das imagens foi

realizada no tipo dinâmico em modo lista, durante 60 minutos, segundo protocolo internacional ADNI (ADNI, 2007).

No segundo dia, o exame foi realizado após a injeção endovenosa, “em bolus”, de PIB, na dose de 459 (± 70) mBq, em participantes que realizaram o jejum de 4 horas e restrição de antiinflamatórios não-esteroidais por 72 horas (AAS não incluído) e as imagens também foram adquiridas em modo lista durante 90 minutos, segundo protocolo internacional ADNI (ADNI, 2007).

4.6.4.2 Processamento e análise unimodal de imagens de PET/CT

Os dados dinâmicos de ambas modalidades de PET foram coletados diretamente da Workstation da máquina de PET/CT, em *list mode*. Todas as imagens foram processadas através da média de captação do radiofármaco de 6 frames de 5 minutos através do software Pmod (versão 3.7, PMOD Technologies Ltd., Zurich, Switzerland), módulo PNEURO, seguindo protocolo indicado pela equipe desenvolvedora. As imagens estáticas de FDG foram geradas a partir do intervalo 30 – 60 minutos após a injeção, enquanto as imagens estáticas de PIB foram geradas a partir do intervalo 40 – 60 minutos para criar uma única imagem média para cada radiofármaco (JACK et al., 2017).

As imagens de ambas modalidades de PET em formato DICOM foram corregistradas com a imagem T1 volumétrica, a qual foi segmentada com amostragem de 6mm e normalizada para o espaço MNI (*template* do Montréal Neurological Institute), usando atlas Hammers-N30R83 para delimitação de ROIs. Foram extraídos todos os ROIs definidos de acordo com as regiões do atlas, como determina o método de máxima probabilidade (HAMMERS et al., 2003). Os valores de captação média de cada região foram calculados em *Standardized Uptake Value* (SUV) em relação à substância cinzenta do cerebelo, formando o *SUV ratio* (SUVr). Foram selecionadas ROIs relacionadas a estudos prévios em Superidosos (DEKHTYAR et al., 2017; HARRISON et al., 2018): Cíngulo anterior presubgenual, cíngulo anterior subgenual, cíngulo anterior, cíngulo posterior (Fig. 9) e hipocampos bilateralmente.

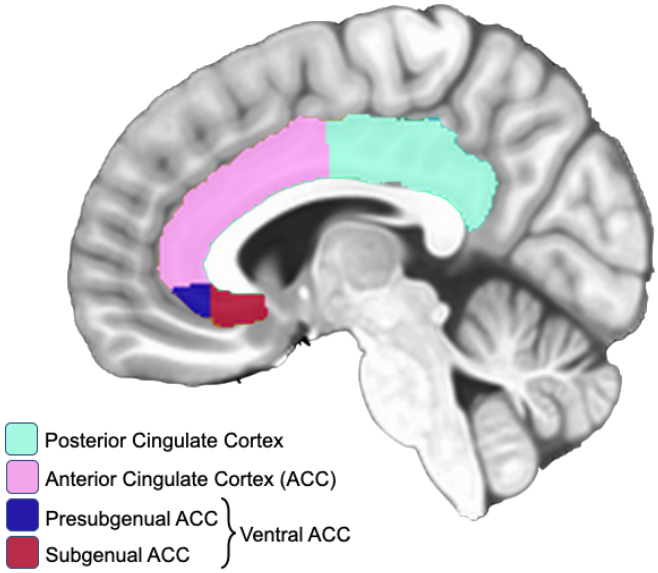

Figura 9. Regiões de interesse delimitadas no atlas Hammersmith N30R83.

Para ambas as análises de PET-FDG e PET-PIB, o valor de SUVr de cada região foi comparado entre os quatro grupos através de ANOVA de uma via, utilizando post hoc de Tukey. Os testes foram corrigidos para múltiplas comparações usando a correção de Bonferroni (10 regiões, $p < 0.005$). Todas as análises estatísticas foram realizadas no software R Studio (v1.0.136), com o pacote Hmisc.

4.6.5. Processamento e análise multimodal PET-FDG e RMf

As imagens de PET-FDG e ReHo coletadas para esse estudo foram processadas de maneira *voxelwise* para fusão multimodal através da análise de componentes independentes conjunta (*Joint Independent Component Analysis*, J-ICA). Os mapas funcionais de ReHo criados a partir da RMf já haviam sido processados dessa maneira (4.6.3.2), porém as imagens de PET-FDG precisaram ser reprocessadas de maneira voxelwise.

Para essa análise, foram utilizadas as imagens PET estáticas descritas previamente (4.6.4.2) e com correção para movimento. As imagens PET/CT foram corregistradas com a T1 volumétrica através do software PMOD. A unidade da imagem foi transformada de Bq/ccm para SUV através do comando 3dcalc (AFNI), onde a matriz da imagem foi dividida pela (dose injetada/peso corporal). A imagem de FDG (agora na escala SUV) foi normalizada para o espaço MNI152 através dos comandos de AFNI 3drefit, 3dresample e 3dNwarpApply para correção do header da imagem, reorientar e adequar de maneira não-linear a imagem ao espaço MNI152, respectivamente. Em seguida, foi feita a normalização voxelwise das imagens em relação ao SUV da substância cinzenta do cerebelo.

As imagens PET-FDG processadas voxelwise foram então utilizadas como input no software FIT toolbox (v2.0, MIALAB) para MATLAB junto com os mapas de ReHo, de acordo com protocolo descrito previamente (SUI et al., 2013). Foi feita a análise de componentes independentes conjunta (J-ICA) para identificar variações conjuntas nessas modalidades que diferenciem o grupo SI do grupo C80. Cada modalidade contribui com uma intensidade de sinal para aquela modalidade, chamado loading factor. Os loading factors foram comparados entre os grupos e foram considerados p-values significativos quando menores que 0,005.

4.7 ANÁLISE ESTATÍSTICA

4.7.1 Cálculo amostral

O cálculo de tamanho amostral para este estudo foi realizado com auxílio do programa R e o pacote estatístico pwr. Baseados no desenho experimental e em dados experimentais prévios (HARRISON et al., 2012) foi calculado um tamanho de efeito de F de 0.5647 (detalhes do teste: significância (α) = 0.05, poder (1-β error probability) = 0.80, parâmetro de não-centralidade δ = 12.75; F crítico = 2.8662; Df = 36; número total da amostra = 40; poder atual = 0.82). Com base nos dados acima expostos, o tamanho amostral foi de 10 indivíduos por grupo.

4.7.2 Análise de dados neuropsicológicos

Os escores dos testes cognitivos foram calculados conforme as instruções de cada teste. Os testes foram então comparados entre os grupos (SA vs. C80, SA vs. C50 e SA vs. DA) com ANOVA de uma via, sendo utilizado o post hoc de Tukey quando adequado. Além disso, os escores do teste de recordação tardia (lista A7 do RAVLT) também foram utilizados como cofator em análise de regressão. Todas as análises cognitivas foram realizadas no software R v1.0.136.

4.7.3 Análise de neuroimagem unimodal e multimodal

Como já descrito nos capítulos acima (4.6.3, 4.6.4 e 4.6.5), os processamentos e análises estatísticas foram realizados com softwares específicos para cada método de imagem. Duas análises foram realizadas para esse estudo: a nível de voxel (Voxelwise) e a nível de ROI. As análises voxelwise utilizam comparação de cada unidade da matriz para comparação entre indivíduos e grupos. A análise a nível de ROI é realizada com a delimitação das regiões de interesse por um atlas, nesse caso o Hammers N30R84.

5 ESTUDOS RESULTANTES DA TESE

Os artigos seguintes foram projetados e escritos como parte integrante deste trabalho. A sequência desenvolvida e posteriormente publicada dos estudos segue a seguinte lógica: Revisão Sistemática de literatura, Definição Operacionalizada, Avaliação de neuroimagem de Superidosos, Avaliação multimodal de Superidosos.

No primeiro estudo, foi realizada uma revisão sistemática de literatura científica para análise de todos artigos com foco em Superidosos e seus sinônimos, como idosos de alta performance cognitiva.

No segundo estudo, foi realizada a definição de idosos de alta performance, devido à alta heterogeneidade de artigos resultantes da Revisão prévia.

No terceiro estudo, foi realizada a avaliação de neuroimagem multimodal, conforme proposto na metodologia desta tese.

No quarto estudo, é apresentado o trabalho resultante do período sanduíche realizado no Nathan Kline Institute for Psychiatric Research, em Nova York. Esse trabalho resultou em um resumo aceito e apresentado na conferência internacional Organization for Human Brain Mapping 2019, em Roma.

Estudo 1. Achados neurobiológicos associados com alta performance cognitiva em idosos: uma revisão sistemática.

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REVIEW

Neurobiological findings associated with high cognitive performance in older adults: a systematic review

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ABSTRACT

Objectives: to perform a comprehensive literature review of studies on older adults with exceptional cognitive performance.

Design: We performed a systematic review using two major databases (MEDLINE and Web of Science) from January 2002 to November 2017.

Results: Quantitative analysis included nine of 4,457 studies and revealed that high-performing older adults have global preservation of the cortex, especially the anterior cingulate region, and hippocampal volumes larger than normal agers. Histological analysis of this group also exhibited decreased amyloid burden and neurofibrillary tangles compared to cognitively normal older controls. High performers that maintained memory ability after three years showed reduced amyloid positron emission tomography at baseline compared with high performers that declined. A single study on blood plasma found a set of 12 metabolites predicting memory maintenance of this group.

Conclusion: Structural and molecular brain preservation of older adults with high cognitive performance may be associated with brain maintenance. The operationalized definition of high-performing older adults must be carefully addressed using appropriate age cut-off and cognitive evaluation, including memory and non-memory tests. Further studies with a longitudinal approach that include a younger control group are essential.

Key words: memory, aging, magnetic resonance imaging

Abbreviations

PET	Positron Emission Tomography
PIB	Pittsburgh compound B
DVR	Distribution volume ratio
AD	Alzheimer's disease
ApoE	Apolipoprotein E

Introduction:

The incidence of dementia has increased in direct proportion to aging in the general population leading to a massive worldwide impact (Prince *et al.*, 2015). As 99.6% of drug therapies for Alzheimer's disease (AD) have not provided promising results (Cummings *et al.*, 2014), different therapeutic targets must be investigated. On the extreme opposite of the cognitive continuum, "Superaging" has become a rising subject of interest as some older adults show exceptional memory ability (Rogalski *et al.*, 2013). Accordingly, individuals that achieve a successful cognitive aging trajectory can either experience less pathological alterations in their brains or show resistance to age-related physiological decline. These older adults with high cognitive performance may exhibit structural and molecular mechanisms that ultimately lead to unusually preserved brain functioning throughout the lifespan.

Older adults tend to show an increased variability of cognitive functions during the aging process (Hedden and Gabrieli, 2004). Currently, many theories of successful aging attempt to explain this vast cognitive variability in older age. There

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are two main theories regarding healthy cognitive aging: the reserve concepts (Stern, 2009) and the brain maintenance (Nyberg *et al.*, 2012). The concept of cognitive and brain reserves has been put forward to explain differences in cognitive decline among older adults, supposed to be a consequence of increased neuronal count and size (Stern, 2009). The amount of reserve may determine the impact of pathological age-related alterations on cognitive and structural phenotypes. However, this definition does not explain why some older adults show cognitive and brain preservation through aging (Habeck *et al.*, 2016).

As a complementary hypothesis to the notion of reserve, Nyberg *et al.* (2012) introduced the notion of brain maintenance. In this conception, structural and functional brain maintenance determines the preservation of memory and other cognitive functions across the lifespan. It poses the avoidance or minimization of the aging brain alterations as best predictors of successful memory abilities in late-life. However, few studies have focused on the biological basis of brain maintenance and its consequences on cognitive aging. Herein, we aim to perform a systematic literature review of studies with older adults with superior cognitive ability to investigate neurobiological findings associated with successful cognitive aging.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher *et al.*, 2009) and was registered at the International Register of Prospective Systematic Reviews, under identification number 42017053255.

Eligibility criteria

Literature search

We performed a search in MEDLINE and Web of Science for pertinent data from January 2002 to November 2017. As we aimed to provide an overview of all available literature, peer-reviewed journals, and grey literature were investigated.

The search strategy included the following key terms: "successful cognitive aging," "high-performing older adults," "SuperAgers," and "exceptional memory capacity." Search terms in Medline also included any of the following Medical Subject Headings (MeSH), and term combinations indicated by "AND" and "OR" were used as Boolean operators: successful OR exceptional OR excellent OR high-performing AND cognition OR cognitive OR memory OR brain AND aging OR superaging OR older adults OR elders OR superagers OR supernormals. The Boolean operators were not used in the Web of Science search due to the structure of its search engine. There were no language restrictions. A meta-analysis was not deemed possible in the present work because of the heterogeneity of the data and the limited number of studies.

Study selection

Two authors (LBF and LP) independently assessed potentially eligible studies for their suitability for inclusion in the review. We resolved any disagreements by discussion or by a third reviewer (WVB). During the screening of titles and abstracts, relevant papers were defined if they mentioned aspects of high cognitive ability, such as "exceptional memory," "exceptional cognition," "excellent memory," and "high-performing." Abstracts were analyzed according to the inclusion criteria, and all studies that met these criteria were included for full article reading.

To recognize subjects within the top level of cognitive capacity in older age, the inclusion criteria were rigorously determined. Articles were required to (1) show original data, (2) include a group of adults who were 70 years of age or older, (3) clearly describe the inclusion criteria for participants, and (4) include individuals in the high-performing group with cognitive score higher than age-matched peers or than that expected for their age group based on normative data. Exclusion criteria were as follows: (1) No clinical characteristics were available, (2) no standardized neuropsychological criteria were used, and (3) any qualitative study.

Extraction of data

Data extraction was conducted by two authors (LP and LBF) from papers that met the inclusion criteria and included the following: demographic characteristics of the sample, the definition used for classifying the high-performing older group, neuropsychological assessments, other inclusion criteria, and main outcomes of each study. To better suit the proposed review, we included only studies with standardized neuropsychological assessment.

Results

Characteristics of included articles

From 4,457 potentially relevant citations retrieved from electronic databases and searches of reference lists, nine (0.2%) studies met the inclusion criteria (Figure 1). There were three studies on

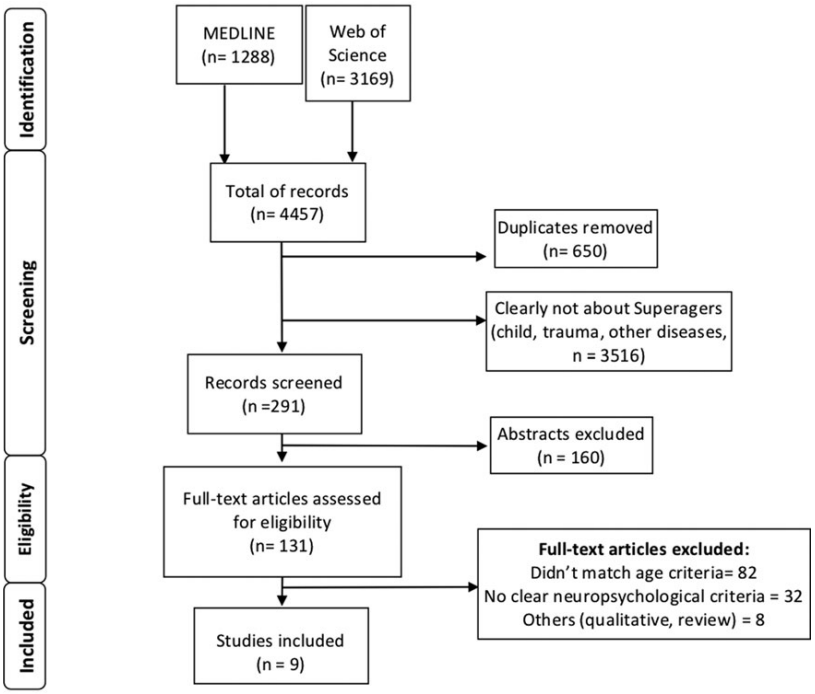

Figure 1. Flow chart of the review.

neuroimaging (Harrison *et al.*, 2012; Cook *et al.*, 2017; Dekhtyar *et al.*, 2017), two on histological analysis (Gefen *et al.*, 2015; Janeczek *et al.*, 2017), one on plasma metabolites (Mapstone *et al.*, 2017), and two on neuropsychological profile (Gefen *et al.*, 2014; Cook Maher *et al.*, 2017). One study reported findings that had been previously published, provided another specific outcome, namely apolipoprotein E (ApoE) status (Rogalski *et al.*, 2013) (Table 1). Sun et al. (Sun *et al.*, 2016) cited the term "SuperAgers" but did not match the age criteria.

Studies that met the eligibility criteria provided a neuropsychological profile of high-performing older adults using either validated tests or at least one control group (Table 2). Sample sizes were related to the type of study (range: 5–330) and all studies reported clinical, neurological, and/or psychiatric screening criteria to confirm a healthy sample. Imaging studies were controlled for sex, age, and education, except Harrison (Harrison *et al.*, 2012) that does not mention the gender of included individuals. Mapstone *et al.* (2017) used a composite Z-score adjusted for sex, age, and education. Histologic outcomes (Gefen *et al.*, 2015; Janeczek *et al.*, 2017) were analyzed only in high-performing females, while the control group included both genders, and Rogalski *et al.* (2013) did not mention this information for ApoE analysis. As seven of the nine studies were conducted by researchers from Northwestern University, the total sample included in this review may overlap some individuals. There were a total of 199 individuals with collected data.

Notably, high-performing older adults were described with different terms, namely "SuperAgers" (Harrison *et al.*, 2012; Rogalski *et al.*, 2013; Gefen *et al.*, 2014; 2015; Cook *et al.*, 2017; Cook Maher *et al.*, 2017; Janeczek *et al.*, 2017), "Supernormals" (Mapstone *et al.*, 2017), and "Optimal performers" (Dekhtyar *et al.*, 2017). All definitions converged in classifying older adults according to their episodic memory performance. The Rey Auditory-Verbal Learning Test was employed in eight of the nine studies, and one study used a composite memory score that included the Memory Capacity Test

Table 1. Summary of included articles

CITATION	TYPE OF OUTCOME	CHARACTERISTICS OF PARTICIPANTS (N)	DEFINITION OF THE HIGH-PERFORMING OLDER GROUP	OTHER INCLUSION CRITERIA	TESTS PERFORMED	MAIN OUTCOMES
Harrison *et al.* (2012)	Structural MRI	HP (12): mean age = 83.5 (3), mean years of education = 14.8 (2.4). YG (14): mean age = 57.9 (4.3), mean years of education = 16.1 (2.9). NC (10): mean age = 83.1 (3.4), mean years of education = 17.5 (2.2)	Age ≥ 80 years Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥9) and within one standard deviation of the average for the non-memory measures	To have preserved activities of daily living and lacked clinical or structural evidence of neurologic or psychiatric disease	RAVLT; BNT; TMT-B; CFT	HP=YG>NC in whole brain volume HP>YG>NC in left anterior cingulate volume
Rogalski *et al.* (2013)	ApoE pattern	HP (12): mean age = 83.5 (3). NC (330): median age = 70	Age ≥80 years Perform at or above average normative values for 50–60 yo (RAVLT delayed-recall raw score ≥ 9) and within one standard deviation of the average for the non-memory measures	To have preserved activities of daily living and lacked clinical or structural evidence of a history of or concurrent neurological or psychiatric disease	RAVLT; BNT; TMT-B; CFT	HP<NC in the frequency of at least one e4 allele (8% vs. 26%)

Table 1. Continued

CITATION	TYPE OF OUTCOME	CHARACTERISTICS OF PARTICIPANTS (N)	DEFINITION OF THE HIGH-PERFORMING OLDER GROUP	OTHER INCLUSION CRITERIA	TESTS PERFORMED	MAIN OUTCOMES
Gefen *et al.* (2014)	Cognitive profile	HP (18): mean age = 82.2 (2.4) *18-month follow-up*	Age ≥80 years Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥9) and within one standard deviation of the average for the non-memory measures	To have preserved activities of daily living and lacked clinical or structural evidence of a history of or concurrent neurological or psychiatric disease	RAVLT; BNT; TMT-B; CFT	HP did not show decline on memory, attention, language or executive function from baseline to 18 months.
Gefen *et al.* (2015)	Histology	HP (5): mean age = 88.6 (5.1), 5F, mean years of education = 17.2 (1.7) NC (5): mean age = 86.6 (8.6), 1M:4F, mean years of education = 13.8(2)	Age ≥80 years Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥9) and within one standard deviation of the average for the non-memory measures	To lack clinical evidence or history of neurologic or psychiatric disease	RAVLT; BNT; TMT-A; TMT-B; CFT; MMSE	Mean numerical estimates of Amyloid plaques and Neurofibrillary tangles density were lowest in HP. HP>YG=NC of Von Economo Neurons in anterior midcingulate cortex, in which neuron density was 3- to 5-fold higher in HP.

Table 1. Continued

CITATION	TYPE OF OUTCOME	CHARACTERISTICS OF PARTICIPANTS (N)	DEFINITION OF THE HIGH-PERFORMING OLDER GROUP	OTHER INCLUSION CRITERIA	TESTS PERFORMED	MAIN OUTCOMES
Mapstone (2016)	Plasma metabolites	HP (41): mean age = 83.2 (3.3), 20M:21F, mean years of education = 16.4 (2.6) NC (41): mean age = 83.2 (3.8), 20M:21F, mean years of education = 16.2 (2.4)	Age ≥70 years. Performed a composite memory Z-score >1.35 SD. Other cognitive functions were required to be > −1.35 SD	To have good overall physical health, visual acuity and hearing sufficient for cognitive testing, proficiency in English language To lack major neurological or psychiatric illness, chronic abnormalities in blood count	RAVLT, FDS (of the WMS-III), TMT-A, TMT-B, BNT, CFT, HVOT	HP>NC in a 12-metabolites panel (Aspartate, Hydroxyhexadecadienylcarnitine (C16:2-OH), 3-Hydroxypalmitoleylcarnitine (C16:1-OH), Lyso PC a C28:1, Arginine, Valerylcarnitine (C5), Lyso PC a C17:0, Asparagine, Citrulline, Nitrotyrosine, PC aa C38:5, and Histamine).
Cook 2017	Longitudinal Structural MRI	HP (24): mean age = 83.3 (3.5), 6M:18F, mean years of education = 15 (2.4) NC (12): mean age = 83.4 (3.8), 7M:5F, mean years of education = 15.6 (4.1)	Age ≥80 years Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥9) and within one standard deviation of the average for the non-memory measures	To have preserved activities of daily living and lacked clinical or structural evidence of a history of or concurrent neurological or psychiatric disease	RAVLT; BNT; TMT-B; CFT	HP<NC in annual percent change of whole-brain cortical volume loss (18 months apart).

Table 1. Continued

CITATION	TYPE OF OUTCOME	CHARACTERISTICS OF PARTICIPANTS (N)	DEFINITION OF THE HIGH-PERFORMING OLDER GROUP	OTHER INCLUSION CRITERIA	TESTS PERFORMED	MAIN OUTCOMES
Dekhtyar *et al.* (2017)	Longitudinal Structural MRI Amyloid PET APOE pattern	HP (25): mean age = 77.5 (6.7), 9M:16F, mean years of education = 16 (6) NC (100): mean age = 78.89 (5.5), 47M:53F, mean years of education = 16 (5)	Age ≥75 years Memory Composite ≥ 0.5 SD. *Maintainers*: three-year follow-up with Memory Composite ≥ 0.5 SD	To have a normal score on the MMSE, Logical Memory II (of the WMS-R) and CDR. To have no history of alcoholism or drug abuse in the last two years, head trauma, or current serious medical or psychiatric illness	Memory composite: delayed scores of the MCT and FNAME. FAS, Letter-number of the WMS-III, DSB, Flanker, TMT-A, TMT-B minus A, Digit Symbol of the WAIS-R	HP > NC hippocampal volumes. HP = NC in level of amyloid burden. HP > NC in Composites of Executive functioning and Processing Speed *Maintainers*: HP = NC hippocampal volumes. HP < NC in level of amyloid burden HP < NC in the frequency of e4 allele (16% vs. 30%)

Table 1. Continued

CITATION	TYPE OF OUTCOME	CHARACTERISTICS OF PARTICIPANTS (N)	DEFINITION OF THE HIGH-PERFORMING OLDER GROUP	OTHER INCLUSION CRITERIA	TESTS PERFORMED	MAIN OUTCOMES
Janeczek *et al.* (2017)	Acetylcholinesterase activity	HP (5): mean age = 90.2 (2.9), 5F NC (15): mean age = 83.3 (8), 9M:6F	Age ≥80 years. Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥ 9) and within one standard deviation of the average for the non-memory measures	To have no indication of ante mortem neurologic or psychiatric disorders	RAVLT; BNT; TMT-B; CFT. Careful chart review if neuro-psychological data not available	HP<NC staining intensity and density of acetylcholinesterase-positive cortical pyramidal neurons
Cook *et al.* (2017)	Psychological well-being	HP (31): median age = 83.4, 17M:23F NC (19): median age = 84.4, 7M:12F	Age ≥80 years Perform at or above average normative values for individuals in their 50s and 60s (RAVLT delayed-recall raw score ≥9) and within one standard deviation of the average for the non-memory measures	To lack clinical evidence of significant neurological or psychiatric illness Maintain their cognitive status from enrollment to the time of questionnaires	RAVLT; BNT; TMT-B; CFT	HP>NC positive relations with others. HP=NC in other subscales of the well-being questionnaire (autonomy, environmental mastery, personal growth, purpose in life, self-acceptance)

Note: HP – High-performing older adults, NC – Normal older controls, YG – Normal younger controls, MRI - Magnetic resonance imaging, RAVLT – Rey Auditory-Verbal Learning Test, BNT – Boston Naming Test, TMT – Trail making test, CFT – Category fluency test, MMSE – Mini-Mental State Examination, FDS – Forward Digit Span, WMS-III – Wechsler Memory Scale – 3rd edition, HVOT – Hooper Visual Organization test, PET – Positron Emission Tomography, MCT – Memory Capacity Test, FNAME – Face Name Associative Memory Exam, WMS-R – Wechsler Memory Scale – Revised; DSB – Digit Span Backwards, WAIS-R – Wechsler Adult Intelligence Scale – Revised, M:F – male:female

Table 2. Characteristics of included articles

	HIGH-PERFORMING OLDER ADULTS	NORMAL OLDER CONTROLS
Number of subjects (range)	199 (5–41)	548 (10–330)
Sex ratio	47M:91F	96M:105F
Mean age (years)	82.5	73.9
Minimum age (years)	77.5	70
Maximum age (years)	90.2	83.7
Mean education (years)	13.6	16
Outcome type (no. of studies)	3 neuroimaging, 2 histology, 1 plasma metabolites, 2 neuropsychological profile, 1 ApoE	
Exclusion criteria	Samples including subjects with <70 years, lack of clear neuropsychological assessment, qualitative studies.	
Measure of cognitive profile	*Episodic memory:* Rey auditory-verbal learning test, delayed scores of the Memory Capacity Test and the Face Name Associative Memory Exam *Other tests:* Logical Memory II, Backward and Forward Digit Span, Boston Naming Test, Trail Making Test (A, B, and A minus B), FAS, Category Fluency Test, Mini-Mental State Examination, Hooper Visual Organization Test, Digit Symbol Test, Flanker Test.	

ApoE – apolipoprotein E, M:F – male:female.

and the Face Name Associative Memory Exam. All included studies reported non-memory tests of the high-performing group similar to normal agers, usually fluency, naming, and attention skills. A longitudinal evaluation showed that most high-performing older adults exhibited no significant cognitive decline in memory and non-memory fields after 18 months of evaluation (Gefen *et al.*, 2014), but two individuals had lower memory scores at follow-up. Besides, this group showed higher level of positive social relationships when compared to age-matched controls, but both groups shared similar well-being score (Cook Maher *et al.*, 2017).

Neurobiological findings of high-performing older adults

Three studies evaluated high-performing older adults using neuroimaging techniques. Positron emission tomography (PET) was used in one paper, while magnetic resonance imaging was performed in all three studies; one had a cross-sectional design (Harrison *et al.*, 2012) and two used a longitudinal analysis with 18 month (Cook *et al.*, 2017) and three year follow-up (Dekhtyar *et al.*, 2017).

High-performing older adults showed global brain volume statistically indistinguishable from that of normal younger controls (average age = 57.9 years), and larger than that of normal older controls (average age = 83.1 years) (average whole-brain volume of High-performers vs. Older controls = 288.05 vs. 244.13 mm^3) (Harrison *et al.*, 2012). Moreover, the high-performing group showed increased thickness of left anterior cingulate (average thickness of High-performers vs. Older controls = 2.75 vs. 2.30 mm^3), and increased hippocampal volumes in comparison to older controls (average volume of High-performers vs. Older Controls = 7,293 vs. 6,883 mm^3) (Harrison *et al.*, 2012; Dekhtyar *et al.*, 2017). An 18-month follow-up showed an annual percent change of the whole-brain cortical volume loss significantly smaller in the SuperAgers group compared to normal older controls (annual percent change of High-performers vs. Older controls = 1.06% vs. 2.24%) (Cook *et al.*, 2017). A PET evaluation with PIB (*Pittsburgh Compound B*) was performed by Dekhtyar *et al.* (2017) and it revealed similar amyloid burden between the high-performing and normal older groups (median Distribution Volume Ratio or *DVR* of High-performers vs. Older controls = 1.16 vs. 1.11). In this same sample, all high-performing individuals whose scores did not decline within three years were classified as maintainers (16 of 25 individuals). This subgroup of maintainers showed lower amyloid burden at baseline compared to non-maintainers (Median DVR of maintainers vs. non-maintainers = 1.11 vs. 1.43), but both subgroups had similar hippocampal atrophy ($p = 0.850$) and amyloid accumulation ($p = 0.257$) rate over three years of follow-up assessment (Dekhtyar *et al.*, 2017).

Mapstone *et al.* (2017) analyzed the plasma metabolome of individuals with high memory capacity. The authors found a panel of 12 metabolites that could distinguish individuals with superior memory from controls, namely aspartate, hydroxyhexadecadienylcarnitine (C16:2-OH), 3-hydroxypalmitoleylcarnitine (C16:1-OH), lysophosphatidylcholine a C28:1, arginine, valerylcarnitine (C5), lysophosphatidylcholine a C17:0, asparagine, citrulline, nitrotyrosine, phosphatidylcholine aa C38:5, and histamine. Interestingly, an index developed with all 12 metabolites showed a significant relationship to a memory composite in the three studied groups. These metabolites also discriminated individuals with cognitive impairment from controls when their signs were reverted.

Two studies evaluated postmortem brain tissues of high-performing elderly individuals (Gefen *et al.*, 2015; Janeczek *et al.*, 2017). Gefen and colleagues reported the last cognitive evaluation of included individuals were within 24 months before death (range = 1–21 months). The authors showed that older adults with youthful memory scores had lower density of neurofibrillary tangles and amyloid plaques than controls in all cingulate areas, except the posterior midcingulate (Gefen *et al.*, 2015). Despite the lower density of pathological deposits, the high-performing group showed mixed Braak staging (from 0 to III). Besides, the anterior midcingulate had higher density of Von Economo neurons in the high-performing group compared to the other group. Total neuronal count and size were similar between the high-performing and control groups. Janeczek *et al.* (2017) evaluated five older adults with high memory performance for density and intensity of acetylcholinesterase (AchE) positivity in pyramidal neurons. They showed significantly lower density of AchE-positive neurons compared to older and younger controls in four described areas, namely the supplementary motor cortex, middle frontal gyrus, middle temporal gyrus, and inferior parietal lobe. The anterior cingulate cortex did not show statistical significance, despite the tendency of decreased density of AchE-positive neurons in the SuperAgers group. The high-performing group also showed decreased intensity in the middle frontal gyrus and middle temporal gyrus in comparison to older controls.

Genotyping for ApoE was described in three studies (Rogalski *et al.*, 2013; Dekhtyar *et al.*, 2017; Mapstone *et al.*, 2017). Rogalski et al. found that the high-performing older group had lower frequency of at least one e4 allele than that seen in normal controls (8% vs. 26%), while the other two studies found no statistically significant differences (16% vs. 30% and 12% vs. 9%).

Discussion

To our knowledge, this is the first review evaluating literature findings of high-performing older adults. Here, we described structural and molecular brain characteristics of individuals at 70 years of age or older with high memory performance compared to age-matched peers. While several studies have focused on successful aging, this review retrieved only studies regarding older adults with superior cognitive performance compared to their cognitively average peers. To select this specific sample, we included all studies that analyzed individuals with memory score of at least one standard deviation above average.

An operationalized definition of high-performing older adults is vital for the generalization of results, including age, cognitive measures, and study design. The age restriction for this review was based on previous studies that related an average onset of age-related memory decline at approximately 60–65 years of age (Rönnlund *et al.*, 2005; Schaie, 2005; Nyberg *et al.*, 2012). We considered 70 years of age an adequate, but not perfect cut-off. A lower limit of age would introduce a bias, while a higher limit would be too restrictive, as aging is a major risk factor for memory decline. Interestingly, episodic memory was measured in all included papers most of them (8/9 studies) used the Rey Auditory-Verbal Learning Test, though episodic memory evaluation was not an inclusion criterion. Typically, episodic memory shows a progressive decrease during the lifespan and it appears particularly vulnerable to aging (Hedden and Gabrieli, 2004; Harada *et al.*, 2013). Episodic memory evaluation at a single point is not a guarantee of cognitive maintenance, as in some high-performers may decline over time (Gefen *et al.*, 2014; Dekhtyar *et al.*, 2017). Non-memory measures were within the age-appropriate average in all included studies. Most studies compared the high-performing group to normal agers, except Harrison that also compared them to a middle-aged group (Harrison *et al.*, 2012). As mentioned by Nyberg *et al.* (2012), older adults with high performance may exhibit a more youthful brain phenotype. Thus, cognitive preservation is better evaluated with longitudinal studies. Moreover, a younger control group may provide important information on brain maintenance, possibly revealing subsequent mechanisms that may replicate memory preservation during senescence.

Despite the small number of studies on older adults with high cognitive performance, this group showed unique structural and molecular features when compared to normal agers. Structural findings of included studies suggest that

excellent memory ability is associated with global preservation of the cortex and decreased age-related atrophy, but it is not related to neuronal size or total count when compared to normal older controls (Harrison *et al.*, 2012; Gefen *et al.*, 2015; Cook *et al.*, 2017; Dekhtyar *et al.*, 2017). These alterations are in accordance with the brain maintenance view, but not with the brain reserve conception. Despite the hippocampal volumes were larger in high performers compared with normal performers, the hippocampal volumes and atrophy rates were similar in three years of follow-up between maintainers and non-maintainers. This finding suggests that the hippocampus is associated with the memory performance, but not with memory maintenance. At a molecular level, high-performing older adults showed lower levels of AD pathology when compared with older adults that showed a decrease in cognitive ability. Despite amyloid accumulation being similar between high-performing older adults and normal controls after three years, those that maintained an exceptional memory ability exhibited lower amyloid deposition at baseline. Neurofibrillary tangles and amyloid plaques were less present in histologic analysis of this group, especially in the anterior cingulate cortex. Moreover, high-performing older adults presented decreased acetylcholinesterase activity in a few brain regions, in contrast to the increase of this enzyme typically seen in age-related cognitive decline (Ashare *et al.*, 2012). Also, plasma metabolites successfully distinguished the high-performing older group from normal agers, indicating peripheral alterations associated with cognitive preservation. Among all metabolites significantly increased in this group, a few were associated with neuroplasticity and cognitive reserve, such as aspartate and NO (Schuman and Madison, 1991; Shimizu *et al.*, 2000; Nikonenko *et al.*, 2013). Consistent with the definition of brain maintenance, these findings suggest that lesser density of age-related lesions is related to better cognition in later life (de Frias *et al.*, 2007).

As proposed by Nyberg *et al.* (2012), structural and molecular preservation may mechanistically impact cognitive functioning. Combined, the findings of included studies on high-performing older adults may provide evidence toward a better understanding of cognitive aging. The maintenance of brain structures shown here may rely upon the marked similarity between brain structures of exceptional agers and younger adults, which are significantly thicker than those of typical older adults (Salthouse, 2009). The persistence of high performance in older adults may result from mitigating neurobiological errors by mechanisms yet to be identified, probably associated with neuroplasticity (Heuninckx *et al.*, 2008; Barulli and Stern, 2013). The avoidance of amyloid pathology, as showed by the subgroup of maintainers (Dekhtyar *et al.*, 2017), may lead to decreased neurodegeneration and consequently higher cognitive functioning. It is putative that both the reserve and maintenance theories converge as complementary concepts (Barulli and Stern, 2013; Habeck *et al.*, 2016). As the adult lifespan is marked by greater cognitive enrichment, the cognitive reserve of high-performing older adults could protect against impairment by reducing age-related pathology to the established networks in older life (Sumowski *et al.*, 2010). However, both reserve concepts do not cover the preservation of cognitive abilities during the aging process (Habeck *et al.*, 2016). However, the current body of literature is insufficient to offer a solid conclusion, as few studies have adequately addressed this group.

Additionally, tau pathology is strongly associated with memory impairment (Riley *et al.*, 2002; Braak *et al.*, 2006). As a single study was inconclusive on tau pathology in autopsies of high-performing older adults, future studies should target tau imaging in this group. Several studies using fMRI have indicated that individuals with age-related cognitive decline rely on compensatory brain activity to preserve function-specific memory networks (Cabeza, 2002; Davis *et al.*, 2008; Park and Reuter-Lorenz, 2009; O'Brien *et al.*, 2010; Eyler *et al.*, 2011). Functional connectivity of high-performing older adults remains unclear, but its elucidation is essential in order to determine the optimal functioning of established neural networks. Both techniques hold great promise in solving the aging brain puzzle.

The risk of biases must be discussed. Despite our efforts, some important papers may have been omitted due to a lack of consensus on the definition of successful aging (Depp *et al.*, 2010; Depp *et al.*, 2011). Further, some studies were not controlled for basic variables, such as sex, especially those including histologic analyses. The total number of studies and the heterogeneity of their results may hinder the generalization of our findings. We performed a comprehensive search with almost no factor of limitation to minimize this bias, but seven of nine included studies were from the same group. Meta-analysis was not possible due to the restricted number of papers on this subject and their heterogeneity of existing papers. Cross-sectional studies are influenced by cohort effects, which can overestimate the study's findings. An estimated prevalence of high-performers is limited in this work because of the design of included studies. Finally, our conclusions may be affected by the small number of studies and its limitations.

In sum, this review draws attention to the study of high-performing, rather than simply healthy, older adults. Despite the insufficient number of studies to draw a consistent conclusion, the compliance of findings in this work corroborates the concept of brain maintenance. High-performing older adults exhibited particular structural and molecular characteristics, such as a preserved cortical volume and decreased AD pathology in the brain. As only few studies provided clear, objective definition criteria for high-performing older adults, further longitudinal investigations with younger controls are necessary to reach concrete conclusions.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

JCC coordinated, designed, and revised this study. WVB designed, analyzed, and contributed in the writing of the manuscript, and the screening of the studies. LP and LBF contributed in the methodology and the screening of the studies. GR contributed with methodological aspects. MWP and LPS contributed to the writing of the manuscript and the review of this study.

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Estudo 2. Definição operacionalizada de idosos com alta performance cognitiva.

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Views & Reviews

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Operationalized definition of older adults with high cognitive performance

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ABSTRACT. Recently, there has been an increasing number of studies on exceptional cognitive aging. Herein, we aim to objectively provide the operationalized characterization of older adults with unusually high memory ability. Some authors have defined them as "SuperAgers", individuals aged 80 years or older with memory ability similar or superior to middle-aged subjects. On the other hand, the terminology "high-performing older adults" (HPOA) seems to appropriately conceptualize these individuals without exaggeration. A threshold for age is not a reliable criterion, but may be defined as 75 and 80 years of age for developing and developed countries, respectively. We propose that HPOA may exhibit episodic memory test scores equal to or greater than those of individuals aged 50-60 years, according to the validated tables for the respective country. This group must also have global cognition scores within expected average values for age and education. Executive functioning may play a central role in the exceptional memory performance of this group. Further studies are essential to confirm existing findings and may provide important evidence for cognitive aging theory and the neurobiology of dementia.

Key words: memory, aging, neuropsychology, older adults, youthful cognition.

DEFINIÇÃO OPERACIONALIZADA DE IDOSOS COM ALTO DESEMPENHO COGNITIVO

RESUMO. O número de estudos sobre envelhecimento cognitivo acima da média vem crescendo recentemente. Neste trabalho, nosso objetivo é fornecer a caracterização operacionalizada de idosos com capacidade de memória excepcionalmente alta. Certos autores definem-nos "Superidosos", indivíduos com 80 anos ou mais com habilidade de memória similar a adultos de meia-idade. No entanto, a terminologia "idosos de alto desempenho" parece definir de maneira apropriada esses indivíduos, sem restrição excessiva. Apesar de um limite de idade ser imperfeito, ele pode ser definido como 75 ou 80 anos, em países em desenvolvimento ou desenvolvidos, respectivamente. Nós propomos que os idosos de alto desempenho devam ter escores em testes de memória episódica de indivíduos entre 50 a 60 anos, de acordo com tabelas validadas para o país. Esse grupo também deve ter escores de cognição global dentro da média para idade e educação. O funcionamento executivo pode ter um papel central no desempenho excepcional de memória desse grupo. Mais estudos são essenciais para confirmar a existência desses achados e podem fornecer evidência importante para teoria de envelhecimento cognitivo e a neurobiologia das demências.

Palavras-chave: memória, envelhecimento, neuropsicologia, idosos, cognição juvenil.

Aging is a major risk factor for many neurodegenerative disorders, particularly Alzheimer's disease. Despite the growing effort in uncovering the underlying pathophysiology of this alarming disease, therapeutic failure has been found to be 99% in all clinical trials.[1] In this context, a different perspective has emerged recently: the study of healthy older adults.[2] Cognitive performance is a major determinant of healthy aging. It is

This study was conducted at the Brain Institute of Rio Grande do Sul (Bralns), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre RS, Brazil.

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well established that cognitive decline leads to overall loss of well-being[3] and functioning in late-life.[4] It is an independent factor of all-cause mortality[5,6] with a massive socioeconomic impact for society[7] and caregivers.[8] Rowe and Kahn's definition of successful aging encompasses a variety of aspects of older adults, including cognition and functioning.[9,10] A more recent and specific terminology, in relation to cognition, "successful cognitive aging" was proposed by Depp.[11] Many cognitive aging theories, such as the concept of cognitive reserve[12] and brain maintenance,[13] have emerged in order to explain why some individuals suffer from age-related decline faster than others. Usually, this theoretical model of aging is applicable to high-performing elderly, whose cognitive abilities appear similar to younger individuals (Figure 1).

Notably, these older adults exhibit similar features to middle-aged individuals.[16] Instead of losing cognitive performance, they seem to be subjected to the underlying mechanisms that minimize the effect of aging, as proposed by the theory of brain maintenance.[13,17] Ultimately, this group presents cognitive maintenance as a major characteristic, which consequently leads to independence and well-being. However, there is a lack of consensus in this field and authors have different opinions on defining and conceptualizing individuals with an exceptional cognitive aging trajectory.[13-15] Inadequate inclusion criteria may possibly bias the external validity of some studies, such as the selection of middle-aged and older adults in the same group.[18] Cognitive assessment is also an issue, as different studies were performed using the same terminology but different cognitive tests.[19-21] As there is a growing interest in the successful cognitive aging trajectory, these biases may profoundly impact the study of the cognitive aging process and its mechanisms of cognitive maintenance.

In this setting, the aim of the present study was to propose an evidence-based opinion of an operationalized definition of individuals who achieve successful cognitive aging and to determine the inclusion criteria for this group, particularly in developing countries.

TERMINOLOGY

As described by Depp et al.,[14] in a review compiling 28 studies, 29 different definitions of successful aging have been proposed so far. As successful cognitive aging is an emerging topic, it has been analyzed from different perspectives leading to numerous different definitions.[19,22,23] Nonetheless, it is essential to conceptualize an operationalized, well-defined age and cognitive measure definition before making assumptions about this group of individuals. In addition, a greater variability in cognitive functioning is found in older age than in the younger population, which may potentially be a confounding factor in cognitive aging studies. Thus, there is a need for a single concept applicable to each specific group.

In this context, perhaps the most popular terminology, "SuperAgers", is defined by individuals aged 80 years or over, with a memory ability similar or superior to middle-aged subjects.[24] Therefore, non-memory domains were evaluated and participants required to perform, on average, within 1 standard deviation on the Trail Making Test Part B, the 30-item Boston Nam-

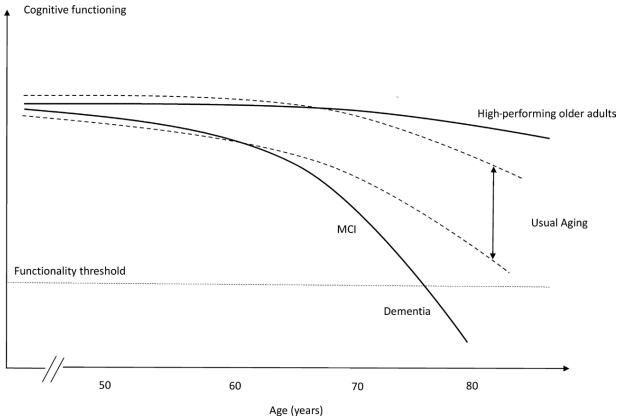

Figure 1. Hypothetical models for different cognitive trajectories of aging.

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ing Test and the Category Fluency Test. Individuals were included when they lacked clinical or imaging findings of neurologic or psychiatric conditions and maintained activities of daily living.

Although this definition is useful in defining older adults with exceptional cognitive ability, we believe it to be rather limited. The evaluation of individuals with high performance does not imply only selecting a single class of subjects with a specific neuropsychological criterion. A broader, more comprehensive definition should also include subjects with little or no literacy but with unusual cognitive functioning. Therefore, the definition of SuperAgers might be inadequate for developing countries, due to the high prevalence of low education and its influence on normative values of cognitive tests. Thus, many individuals who are not classified as SuperAgers, but have exceptional memory ability for age and education, might be misclassified as usual agers.

There is a significant effort to elucidate the aging process by studying cognitively average older adults. Selection criteria of many studies includes older adults without signs of cognitive decline.[25-27] Nonetheless, these individuals present typical age-related cognitive decline. Here we focus on individuals with cognitive performance that is above average for their age. These individuals potentially have maintained their memory ability throughout the aging process, scoring similar to middle-aged subjects.

We propose a general nomenclature for individuals who achieve successful cognitive aging. The term "High-performing older adults" (HPOA), first cited by Cabeza et al.,[19] provides an expanded concept of individuals who maintain unusually good cognition. Although some studies have used the same terminology, their selection criteria were not the same. While some studies used memory scores for defining HPOA,[16,19,24] others used educational level or non-memory domains.[20,21,28,29] The heterogeneity of previous studies supports the need for a single terminology and evidence-based criteria for classification of HPOA. Imperative for this definition, we propose two main features for classifying an individual as HPOA, namely suitable age threshold and adequate cognitive measurements, either of memory or non-memory domains.

AGE CUT-OFF

An adequate age criterion is vital for proper selection of older individuals with high cognitive performance. Different age criteria are used by different authors, ranging from 60 to 80 years.[16,22,30,31] Since this limit appears to vary substantially across studies, we suggest that a single age limit for defining HPOA can benefit further generalization of results.

The concept of aging is cultural and dynamic. The onset of old age is a matter of discussion, with a massive impact on public health policies, labor force, and retirement. Conventionally, aging is arbitrarily determined as occurring at 65 and 60 years of age in developed and developing countries, respectively.[32,33] The World Health Organization (WHO) and the Brazilian Elderly Statute use the standard of age 60 to describe older adults, but the WHO clarifies that this is not a precise cut-off.[34] Moreover, aging is directly affected by life expectancy, which plays a major role in this definition. Individuals born in resource-rich countries have a higher possibility of attaining an older age. An individual born in the United States, for both sexes, lives almost five years longer when compared to a Brazilian subject (79.3 vs. 75).[35]

Age-related cognitive decline usually intensifies at around 60-65 years of age[13] and should be carefully addressed in cognitive aging studies. Longitudinal and cross-sectional samples indicate that between 20-60 years there is little or no cognitive decline,[36,37] but it is marked after the age of 74 years.[38] Age-related brain atrophy follows a non-linear process, in which prefrontal and parietal regions are more vulnerable.[39-41] Grey matter density of cognitively normal adults also undergoes more rapid decline from 7 to 60 years, with lower atrophy rates thereafter.[42] Studies that include individuals aged 60 to 65 years may introduce a bias, as age-related cognitive decline is already underway. Hence, it is believed that individuals who do not suffer from age-related cognitive decline up until 75 years of age have a higher likelihood of maintaining their cognitive ability, given that they do not have neurological diseases causing cognitive impairment or dementia.

The HPOA age cut-off may vary according to sociodemographic and cultural characteristics. We propose a threshold of successful cognitive aging according to sociocultural characteristics of the studied sample. An adequate, though imperfect, cut-off could be determined for the developed and developing countries as 80 and 75 years, respectively. These proposed cut-offs account for the 5-year difference both in life expectancy and in the definition of older adults between developed and developing countries, as previously cited in this topic. Furthermore, developing countries have lower educational levels and higher social discrepancy than developed countries. Thus, a higher age threshold may incorrectly select individuals with a better educational and economic background in these nations.[43-45]

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COGNITIVE CRITERIA

Memory scores

The extent of usual, age-related cognitive decline implies a subject's ability for independence and functioning in daily life. The processes of memory encoding, storage, and retrieval decline over the course of the whole lifetime, where encoding is particularly vulnerable to aging and seems to decline across the lifespan.[36] The encoding of novel memories is a major hippocampal function and shows a strong relationship with memory impairment in AD.[46-48]

Several studies regarding high performance in old age rely upon episodic memory evaluation as a major defining factor.[16,22,23,49] In agreement with other studies in this field, the definition of HPOA must consider episodic memory performance as essential because of its clear relationship with cognitive impairment and dementia. Besides, the biological mechanisms of HPOA may differ to that of AD-type dementia given their contrasting clinical features. A cognitive composite of executive functions, memory, and global cognition reliably determines the first signs of AD,[50] which highlights the importance of these functions in this condition.

There are several validated and reliable tools for episodic memory measurement in the English language. Specifically, psychometric properties for Brazilian neuropsychological tests lack diversity and adequacy of data. The Rey Auditory-Verbal Learning Test (RAVLT), typically applied in older adults, reliably distinguished not only high-performing groups from controls[51] but also different age groups.[52,53] This tool also showed good replicability in distinguishing normal from pathologic cognitive decline with aging.[54] However, the Brazilian population tends to be penalized due to lack of suitable scores for low levels of education on the RAVLT.[52] In this context, visual memory tasks may be useful, such as the visual task of the Brief Cognitive Screening Battery[55] and the Rey-Osterrieth Complex Figure.[56] Visual memory tasks have shown little association with the educational level of individuals,[57,58] while reliably measuring their memory performance.

There are many factors that must be considered when choosing the adequate neuropsychological test to measure episodic memory capacity. The major factor in considering any test is the development of normative data for the studied population. There are many suitable tests developed specifically for measuring verbal memory (Table 1), such as the California Verbal Learning Test[59] (not available for the Brazilian population) and the Free and Cued Selective Reminding Test,[60] for example. Some tests are commonly used in Brazil, but their references are standardized scores validated for the North American population, such as the Wechsler Memory Scales.[61]

As defined in previous studies, HPOA must represent the highest level of memory performance in elderly. Some studies define the top 20% of the sample as high memory performers, which may introduce a bias. This method selects only high performers in a single sample, which may not adequately represent the high-performing individuals in the general population as a whole.

Nonetheless, the rigid memory score definition used by Rogalski et al.,[24] greater than or equal to the normative values of individuals at 50-60 years, is adequate for several reasons. First, this age range considers the memory scores of individuals before the typical age-related memory decline, as described in Topic 2. Second, as it is related to the test, this method of selecting HPOA is independent of sample size. Third, it facilitates the comparison of data with studies from other contexts

Table 1. Commonly used memory tests for the Brazilian population.

Cognitive test	Category evaluated
Rey Auditory-Verbal Learning Test	Verbal
Free and Cued Selective Reminding Test (free delayed-recall)	Verbal
Logical Memory Immediate and Delayed Recall (WMS III)	Verbal
California Verbal Learning Test *	Verbal
Hopkins verbal learning test	Verbal
Rey-Osterrieth Complex figure	Visual
Visual Memory Index (WMS III)	Visual
Brief Cognitive Screening Battery	Visual

*Normative data not available for the Brazilian population.

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and cultures that also define HPOA as older adults scoring greater than or equal to individuals of 50–60 years. Thus, we propose that HPOA may be selected with a memory test score that is equal to or above normative values of individuals at 50–60 years of age, but not necessarily using the RAVLT. Individuals with low educational level may be evaluated with visual memory instead of verbal memory tests (Table 1).

Non-memory scores

Global cognition must also be evaluated in order to successfully select individuals with excellent memory performance. A low score on this type of test may indicate a subclinical pathologic process that does not affect the memory system. On the other hand, above average scores suggest that these individuals have an optimal performance when associated with unusually high memory scores. It is important to note that the cognitive evaluation typically performed in a neurological or psychiatric routine is essentially not a measure of global cognition. Some tools for dementia screening are excellent for the diagnosis of mild cognitive impairment or dementia staging but should be avoided as classifiers for "cognitively normal", such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA).[62] A comprehensive and validated tool may be used for classifying subjects, such as the Addenbrooke's Cognitive Evaluation-Revised or the Mattis Dementia Rating Scale.[63,64]

Frontal lobe functioning seems to be particularly vulnerable to aging.[27,36] Previous studies indicate that attention is essential for memory formation and precedes memory consolidation.[65-67] Furthermore, inhibitory control, a component of the attentional system, shows an exacerbated decrease after 60 years of age,[68] although this does not affect selective attention.[69] The frontostriatal system may be the major cause of decline in executive functioning in nondemented individuals; this has an indirect but strong impact on memory encoding.[36,70] White matter also seems to be preferentially weakened in anterior tracts.[71,72] Executive functioning in HPOA is still open to debate, as a recent study suggests that a group of cognitive maintainers may rely upon frontal mechanisms for memory maintenance.[22] Accordingly, the anterior cingulate is associated with the cognitive control and regulation of attention,[73-75] which corroborates that it may play a key role in the exceptional memory in HPOA.[16,22]

Processing speed is a strong indicator of age changes in memory ability[76] and also seems to be associated with HPOA.[22] Some functions appear to be less vulnerable to age-related cognitive decline, such as semantic memory, vocabulary, and fluency skills. Both are linked as crystallized intelligence and tend to enhance with aging.[27,77,78] However, it is believed that these functions are not central to cognitive maintenance in aging.

UNANSWERED QUESTIONS AND LIMITATIONS

A complete understanding of the mechanisms at play in older adults who successfully preserve their memory may reveal key processes in cognitive maintenance. There is still a lack of knowledge in understanding usual and unusual aging. Some recent studies have focused on preclinical stages of Alzheimer's disease in order to discover early biomarkers of memory decline. The promotion of successful cognitive aging holds great promise in targeting biomarkers, potentially improving cognitive function in later life.

The frontal lobe has been shown to be particularly vulnerable to aging and neurodegenerative processes.[36] Only one study evaluated executive functioning in HPOA and showed an intriguing preservation of these functions.[22] Further, subdomains of attention have not been explored in HPOA to date. Further investigations involving frontal assessment tests are needed to better elucidate the role of executive functions and processing in HPOA.

Some neuropsychological tests are not available in many languages. There is a preference for the evaluation of specific cognitive domains in clinical practice, which may imply a misuse of non-culturally adapted versions of tools. Thus, translation, validation, and development of normative values are needed in order to reliably measure the cognitive functioning of older adults, which must be based on cultural and demographic factors.

There is still a need for longitudinal studies on HPOA. Individuals with high cognitive performance may have progressive decline, which is not measurable using a cross-sectional design. In addition, it is not yet known if HPOA cumulate a higher cognitive reserve than usual agers or its relationship to brain maintenance. Only by carefully addressing studies on cognitive aging, will we be able to advance in distinguishing preclinical AD from usual cognitive aging.

CONCLUSION

In summary, in this study we proposed an evidence-based selection criteria for older adults with exceptional cognitive performance. This study plays a role in defining these individuals according to age and cognitive criteria (Table 2), in contrast with the heterogeneity of studies using different measures and terminologies. With a

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Table 2. Operationalized definition of High-performing older adults.

	Age	Memory test scores	Non-memory test scores
Developed countries	≥ 80	Aged ≥50-65 years	Within expected average for age and education
Developing countries	≥ 75		

single concept of HPOA, this study may provide support to better understand the cognitive aging process.

Author contributions. Wyllians Vendramini Borelli, Karoline Carvalho Carmona and Adalberto Studart-Neto contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content. Ricardo Nitrini, Paulo Caramelli and Jaderson Costa da Costa contributed to drafting and critical revision of the manuscript for important intellectual content.

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Estudo 3. Correlatos neurais da habilidade excepcional de memória em SuperIdosos: Uma abordagem multimodal usando FDG-PET, PIB-PET e MRI.

Este artigo foi submetido como *Preprint* no site BioRxiv.com e submetido posteriormente para publicação no periódico *Neurobiology of Aging*, atualmente em processo de revisão.

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Abstract: Individuals at 80 years of age or above with exceptional memory are considered SuperAgers (SA). A multimodal brain analysis of SA may provide biomarkers of successful cognitive aging. Herein, a molecular (PET-FDG, PET-PIB), functional (fMRI) and structural analysis (MRI) of SA was conducted. Ten SA, ten age-matched older adults (C80) and ten cognitively normal middle-aged adults underwent cognitive testing and neuroimaging examinations. The relationship between cognitive scores and cingulate areas and hippocampus were examined. The SA group showed increased FDG SUVr in the left subgenual Anterior Cingulate Cortex (sACC, $p<0.005$) as compared to that in the C80 group. The SA group also presented decreased connectivity between left sACC and posterior cingulate ($p<0.005$) as compared to that of C80 group. Amyloid deposition was similar between SuperAgers and control groups in the described regions or overall areas ($p>0.05$). These results support the key role of ACC in SA, even in the presence of amyloid deposition. It also suggests that sACC can be used as a potential memory biomarker in older adults.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

Cover Letter

June 12, 2019

Peter R. Rapp
Editor-in-Chief
Neurobiology of Aging

Dear Editor:

I wish to submit an original study for publication in *Neurobiology of Aging*, titled "Neural correlates of exceptional memory ability in SuperAgers: A multimodal approach using FDG-PET, PIB-PET, and MRI."

In this study, we performed a multimodal neuroimaging evaluation of SuperAgers (SA). By definition, this group of individuals exhibit exceptional memory skills at an older age. We examined the relationship between cognitive scores and cingulate areas and hippocampus, as previous studies suggested that these regions present unique features in SA. The SA group showed increased metabolic activity in the left subgenual Anterior Cingulate Cortex compared with normal agers, among other significant relations between their delayed-memory scores and other subareas of the Anterior Cingulate. Importantly, the metabolic activity of subgenual Anterior Cingulate Cortex of SA was similar to a group composed by middle-aged individuals. However, amyloid deposition was similar between SA and normal agers. SA individuals also showed increased connectivity in frontal regions when compared with normal older adults.

Further, we believe that this paper will be of interest to the readership of your journal because it provides evidence for the cognitive aging process and further studies on successful cognitive aging.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
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***Highlights (for review)**

Highlights

- SuperAgers show increased metabolic activity in left subgenual anterior cingulate;
- Subareas of anterior cingulate are associated with delayed-recall memory scores;
- SuperAgers exhibit increased functional connectivity of frontal areas;
- Amyloid deposition is similar between SuperAgers and normal agers.

Neural correlates of exceptional memory ability in SuperAgers: A multimodal approach using FDG-PET, PIB-PET, and MRI.

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Abstract:

Individuals at 80 years of age or above with exceptional memory are considered SuperAgers (SA). A multimodal brain analysis of SA may provide biomarkers of successful cognitive aging. Herein, a molecular (PET-FDG, PET-PIB), functional (fMRI) and structural analysis (MRI) of SA was conducted. Ten SA, ten age-matched older adults (C80) and ten cognitively normal middle-aged adults underwent cognitive testing and neuroimaging examinations. The relationship between cognitive scores and cingulate areas and hippocampus were examined. The SA group showed increased FDG SUVr in the left subgenual Anterior Cingulate Cortex (sACC, $p<0.005$) as compared to that in the C80 group. Amyloid deposition was similar between SA and C80 in the described regions or overall areas ($p>0.05$). The SA group also presented decreased connectivity between left sACC and posterior cingulate ($p<0.005$) as compared to that of C80 group. These results support the key role of ACC in SA, even in the presence of amyloid deposition. It also suggests that sACC can be used as a potential memory biomarker in older adults.

Keywords: SuperAgers; high-performing older adults; successful cognitive aging; FDG; amyloid deposit; MRI

Abbreviations: BCa – Bias corrected accelerated; SA–SuperAgers; C50–Middle-aged controls; C80–Age-matched controls;

1. **Introduction**

SuperAgers (SA) is a definition to describe individuals who have achieved successful cognitive aging (Borelli et al., 2018a). By definition, SA are individuals aged 80 years or more, exhibiting higher youthful memory scores, which are similar to those of younger individuals who are 50 to 65 years old (Harrison et al., 2012). A review that presents the unique brain morphology and function of SA has been recently published (Borelli et al., 2018b). SA show an increased cortical thickness in the anterior cingulate, similar global amyloid burden and lower volumes of white matter hypointensity, as compared to that of normal aged individuals (Baran and Lin, 2018; Harrison et al., 2018). Whether SA activates compensatory mechanisms or they exhibit youthful brain features is a rather controversial topic.

Glucose brain metabolism can be measured by Positron Emission Tomography (PET) using the radiotracer ^{18}F-Fluorodeoxyglucose (FDG) (Knopman et al., 2014). This ligand has clinically been used as an important biomarker in Alzheimer's Disease (AD) (Mosconi et al., 2008; Noble and Scarmeas, 2009) and can be used to measure the decrease in brain activity resulting from normal aging process. Although a reduction in whole-brain glucose metabolism is observed in older adults, the magnitude of decrease differs depending on the region (Nugent et al., 2014). Healthy older adults exhibit significant hypometabolism in the medial frontal regions such as the anterior region of the cingulate, as compared to that in the younger controls (Ishibashi et al., 2018; Pardo et al., 2007; Yoshizawa et al., 2014). A study reported that high-performing older adults exhibited increased prefrontal FDG uptake as compared to their age-matched peers (Cabeza et al., 2002), suggesting that these individuals are less affected by age-related hypometabolism. However, the findings of these participants were not compared to a younger group that would have confirmed whether or not SA exhibited preserved brain metabolism.

Abnormal deposition of amyloid plaques is strongly associated with Alzheimer's disease spectrum (Jack et al., 2018). A few recent PET studies investigated the amyloid burden in older adults with normal and high cognitive performance using the radiotracer ^{11}C-Pittsburgh Compound B (PIB) (Donohue et al., 2017; Jansen et al., 2015; Villemagne et al., 2011). These studies have shown that

amyloid-positive older adults exhibited increased rates of cortical atrophy and cognitive decline but decreased regional glucose metabolism in comparison to the amyloid-negative older adults. Older adults with exceptional memory capacity presented mixed findings of brain amyloid load as compared to that of the other normal individuals for that age (Baran and Lin, 2018). However, another follow-up study noted that individuals who maintained their cognitive scores had lower amyloid deposition after three years as compared to individuals whose cognition was declined (Dekhtyar et al., 2017).

Resting-state functional magnetic resonance imaging (rsfMRI) has been shown to be highly accurate in predicting functional connectivity (FC) abnormalities related to the aging process (Iraji et al., 2016). A significant decrease in FC is expected in healthy individuals as they age (Marques et al., 2015), though some brain networks of older adults, involving frontal and temporal areas, are particularly affected (Dennis and Thompson, 2014; Lopez-Larson et al., 2011). The Default Mode Network (DMN), typically associated with memory system and self-thoughts, has been demonstrated to be affected by age-related cognitive decline, thus presenting reduced FC between the anterior cingulate and posterior cingulate in older individuals (Dennis and Thompson, 2014; Koch et al., 2010). Previous studies have highlighted the pivotal role of cingulate regions in successful memory encoding (Grady et al., 2003; Lee et al., 2016) and retrieval (Lega et al., 2017).

Nonetheless, it is not possible to completely evaluate the complexity of human cognitive processes using a single method of analysis. Besides, combining multiple features provided by modality-specific techniques can help improve the overall understanding of the neural basis of successful cognitive aging and SuperAging. Considering the fact that decreased functional activity and altered molecular properties of the brain are expected during the aging process, how these changes relate to each other is still unclear. The aim of the present study was to analyze the changes in the brain in regional glucose metabolism, functional connectivity, amyloid burden and structural characteristics of SA. A multimodal neuroimaging approach (FDG-PET, PIB-PET, functional MRI, and structural MRI) was thus applied to compare SA with a younger, middle-aged control group.

2. **Methods**

2.1. Participants

Community-dwelling older and middle-aged adults were evaluated at the Brain Institute of Rio Grande do Sul (BraIns). Individuals were invited via the social media, television advertisement, and also through courses in the university that are focused toward the elderly. The participants included in the study were right-handed individuals with no history of substance abuse, moderate or severe head trauma or serious neurological or psychiatric diseases. All the participants included in the study denied any family history of dementia or cognitive impairment. They also demonstrated preserved daily life activities and negative scores for the Geriatric Depression Scale (raw score < 5) (Yesavage and Sheikh, 1986). Prior to their enrolment into the study, all the participants signed an informed consent form, previously approved by the university's ethical committee. These participants were then divided in three groups: SuperAgers (SA), Age-matched Controls (C80) and Middle-aged Controls (C50).

The SA group was defined on the basis of previously described criteria (Harrison et al., 2012). This group comprised older adults aged 80 years or above, who showed the ability to a) perform at or above the normative values determined for individuals between 50 to 65 years of age on the delayed-recall score of the Rey Auditory-Verbal Learning Test (RAVLT), and b) perform at or above normative values determined for their age and education in non-memory domains. Non-memory measures included the Mini-Mental State Examination (MMSE), the Trail-Making Test – Part B (TMT-B), the Category Fluency Test–Animals (CFT) and the Boston Naming Test (BNT). Two healthy control groups, comprising age-matched individuals who were running in their 80s (C80) and cognition-matched individuals running in their 50s (C50) were also included in the study. The participants included in both the control groups were required to perform within a normal range in both, memory and non-memory fields, with 1.5 as standard deviation from the mean, using normative values for age and education. A fourth group was selected for comparison purposes, which comprised individuals at a mild stage of Alzheimer's Disease (AD) following previously established diagnostic criteria (NIA-AA) (McKhann et al., 2011). This group was included to demonstrate extreme, opposite biomarker values compared to the SA and control groups; however, this was not included in the discussion. All the study individuals underwent three imaging sessions, FDG-PET, PIB-PET, and MRI (Fig. 1).

Figure 1. Schematic diagram of the study protocol.

2.2. Image acquisition and pre-processing

PET imaging

PET scans were performed within five months of clinical screening and cognitive testing. Both FDG and PIB measurements were performed using a GE Discovery 600 scanner. First, a regular CT scan was obtained for attenuation and scatter correction. Subsequently, PET data were acquired using 3D list-mode. The data were reconstructed using VUE Point HD (2 iterations, 32 subsets, filter cutoff 4.8 mm, matrix size 192 × 192 × 47, voxel size 1.56 × 1.56 × 3.27 mm) and corrected for attenuation, scatter, dead time and decay. Before performing PET scans, an intravenous catheter was placed in the left arm of all the patients and their heads were immobilized in order to minimize motion during the scan.

Participants were instructed to follow a low glucose diet 24 hours prior to the FDG scan, in which the last 4-hours consisted of fasting. Before injection, the participants were made to rest for 30 min and capillary glucose was measured 10 min prior to the PET scan, with acceptable levels ranging between 70 and 120 mg/dL, before imaging acquisition. The radiotracer was injected in bolus (326 ±47 MBq) and a list-mode dynamic emission scan was performed in 60 min. For the PIB scan also, the participants were made to follow a 4-hour fast. PIB was injected intravenously (459 ±70 MBq) in bolus, while the participants were positioned inside the scanner and a dynamic list-mode acquisition was performed in 90 min.

Static PET images were acquired using raw dynamic frames (6 × 5 min frames) at 30–60 min post-injection for FDG and 40–60 min post-injection for PIB, which were averaged to create one single averaged image. Rigid co-registration of individual data (PET and MRI) was performed using a normalized mutual information algorithm, and the maximum probability atlas (Hammers N30R83) was used for the generation of standard brain regions of interest (ROI) in PNEURO tool (version 3.8, PMOD Technologies Ltd., Zürich, Switzerland).

MR imaging

MR structural and functional images were collected on a GE HDxt 3.0T MRI scanner with an 8-channel head coil. A T1-weighted MPRAGE-similar volumetric sequence designed for GE was acquired using 3D FSPGR BRAVO (TR = 6.27ms; TE = 2.25 ms; TI = 550 ms; Flip Angle = 11˚; matrix size 512 × 512 × 196, voxel size 0.5 × 0.5 × 1.0 mm). These images were used for co-registration with other imaging modalities, tissue segmentation, and definition of ROIs. The echo-planar sequence (EPI) was acquired during a 7-min resting-state protocol (TR/TE=2000/30ms, matrix size 64 × 64, FOV 64 × 64, total volumes 210). During the functional scan, the participants were requested to stare at a crosshair and not to think of anything in particular. A real-time operating system was used to monitor the head motion of the study participants. The participants who moved their heads excessively were reminded to maintain their heads still, and the sequence was restarted.

All functional images were pre-processed using the software AFNI (afni.nimh.nih.gov) (Cox, 1996). Preprocessing steps included slice-time and motion correction and a non-linear spatial normalization to 3.5 × 3.5 × 3.5 mm^3 voxel template (MNI152 template). Time Repetitions (TR) tracked with excessive motion [Framewise Displacement (FD) > 0.6 mm], were censored from the dataset. The exclusion criterion for the excessive motion was defined to be the motion wherein a participant had 20% of the TRs above the FD threshold. A nuisance regression with six motion estimated parameters (x, y, z, roll, pitch, yaw) and time-series of the average signal of the white matter and cerebrospinal fluid was performed. Signal detrending using a bandpass temporal filter (0.01 and 0.1 Hz) (Weissenbacher et al., 2009) and smoothing with a 6 mm FWHM Gaussian kernel were also employed as preprocessing steps on the functional data.

2.3. Neuroimaging Data Analysis

PET Imaging

For both FDG and PIB, anatomical ROIs were generated using the Hammers N30R83 brain atlas (Hammers et al., 2003). The Standardized Uptake Value (SUV) was obtained by normalizing tissue concentration to the injected dose and body weight. ROIs were analyzed bilaterally (Gousias et al.,

2008; Hammers et al., 2003). The Standardized Uptake Value Ratio (SUVr) was calculated using the cerebellum grey matter as reference (M Bauer et al., 2013), for both FDG and PIB. For PIB images, an adaptation of the AD-signature ROI composite (Jack et al., 2017) was accomplished using the average of the mean uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs. Whole-brain cortical SUVr was measured for FDG analysis. Cingulate regions and hippocampus SUVr were analyzed for both the PET modalities.

MR Imaging

Seed-based analysis

A seed fMRI (functional MRI) analysis of connectivity was performed, based on previously described regions that distinguished SA from other normal individuals of that age (Baran and Lin, 2018; Harrison et al., 2012). ROIs were extracted by using regional boundaries of the Hammers brain atlas for the following regions: anterior cingulate, posterior cingulate, presubgenual and subgenual areas (Fig. 1: Supplementary material). For each participant, the average time course of the voxels within the seed was collected, and Pearson's correlation was implemented between the time series of each ROI and all other voxels in the brain. Correlation results were then remodeled using Fisher's r-to-z method, prior to the statistical analysis.

Independent Component Analysis

The data-driven model analysis was also carried out for the rsfMRI with Independent Component Analysis (ICA) using MELODIC (FSL, v6.0.0). Fourteen components were estimated for this analysis, which successfully distinguished resting-state networks; dual regression was applied to identify the independent component (IC) maps in each individual. IC-6 was selected because of significant activation of hippocampal and cingulate areas (Fig. 4).

Structural MRI analysis

Cortical thickness and volume were calculated using the image analysis software FreeSurfer (version 6) (Fischl and Dale, 2000). All images were processed by running the "recon-all" script with default

settings. Manual corrections were performed for segmentation and parcellation errors, described as a priori by https://surfer.nmr.mgh.harvard.edu/fswiki. This method has been demonstrated to be reliable and was validated with similar accuracy as that of manual segmentation of grey and white matter (Rosas et al., 2002).

2.4. Statistical analysis

The normality of the sample was calculated using the Shapiro-Wilk test. ANCOVA and ANOVA calculations followed by Tukey's post-hoc test were performed to compare SA with other groups for the statistical analysis of FDG-PET and PIB-PET (R Studio – v1.0.136). The seed-based and IC analysis were performed using AFNI's scripts for group comparison, general linear model fitting (*3dMVM*), and regression analysis (*3dRegAna*) (Cox, 1996). The results were considered to be statistically significant ($\alpha<0.05$) for a minimum cluster size of 1498 μL and a threshold of $p<0.005$. The structural MRI analysis (cortical thickness and average volume) was performed using the QDEC interface from Freesurfer. Statistical tests for structural measures were corrected for multiple comparisons using Monte Carlo Simulations (Freesurfer).

Pearson's correlation tests were employed to measure the relationship between cognitive scores and neuroimaging metrics. Each of these tests used bias-corrected accelerated (BCa) 95% confidence intervals (CI) and 1000 Bootstrapped samples to create a re-sampled range of correlated coefficients. The effect size of all associations was also calculated using Cohen's d. Multiple linear regressions were performed to calculate the associations between cognitive scores and neuroimaging metrics. All ROI-wise and regression analysis were performed using the R Studio (v1.0.136).

3. **Results**

3.1. Demographic factors

No significant differences were found between SA and C80 group in terms of age, years of education or distribution of sex (Table 1). Although C50 group differed from SA group in terms of age, as

expected by the inclusion criteria ($p < 0.001$); yet, education, sex, and cognitive measures did not differ statistically between these groups ($p > 0.05$ for all measures).

Table 1. Demographic Characteristics of the participants.

	SA	C80	C50	AD	SA vs. C80 p-values	SA vs. C50 p-values
Demographic						
Age (years)	82.1 (±2.5)	84.2 (±3.6)	58.5 (±5.8)	84.4 (±3.6)	0.66	<0.001
Sex (M)	7 (70%)	6 (60%)	8 (80%)	5 (55.6%)	0.62	0.6
Education (years)	12.7 (±4.8)	12.9 (±5.0)	14.2 (±4.9)	11.9 (±5.3)	0.99	0.91
Cognitive scores						
MMSE	28.7 (±1.3)	27.9 (±1.2)	29.5 (±0.7)	19.4 (±5.4)	0.91	0.91
Delayed-recall scores	11.4 (±2.0)	6.9 (±1.6)	10.7 (±3.4)	0.3 (±0.5)	**0.0002**	0.86
BNT	57.5 (±1.8)	54.5 (±2.7)	56.4 (±3.4)	47.9 (±8.8)	0.51	0.95
CFT	20.5 (±3.6)	16.8 (±8.9)	19.5 (±3.1)	10.4 (±3.0)	0.41	0.97
TMT-B	123.3 (±40.2)	146.9 (±64.4)	93.3 (±55.2)	278.1 (±65.7)	0.79	0.64

SA: SuperAgers; C80: Control–80 years; C50: Controls–50 to 65 years; AD: Alzheimer's Disease; MMSE: Mini-mental state examination; BNT: Boston Naming Test; CFT: Category Fluency Test; TMT-B: Trail-Making Test – Part B.

3.2. PET results

Brain glucose metabolism

SA group showed significantly increased metabolic activity in sub-regions of the Anterior Cingulate Cortex (ACC), especially the left subgenual ACC (sACC, Table 2), as compared to that in C80 group. The right pre-subgenual region of the ACC (pACC) showed increased brain activity in SA as compared to that in C80 group; however, this relation was later corrected for multiple comparisons (1.02 ±0.08 vs. 0.88 ±0.07, $p < 0.01$ uncorrected) and did not survive long. Subsequently, sACC and pACC were grouped in a single ROI named ventral anterior cingulate (vACC, Fig. 1 Sup. Material). The SA group showed increased FDG SUVr for both, right and left hippocampal regions as compared to the C80 group (Table 2) but not with C50 group ($p > 0.05$). These tests did not pass corrections for multiple comparisons.

Importantly, all described regions of the anterior cingulate cortex (including the vACC) and hippocampus exhibited similar metabolic activity between the SA and C50 groups ($p > 0.05$). In comparison to SA, the AD group showed statistically decreased FDG SUVr for all measures, except for the left ACC, right ACC, left vACC, and right vACC ($p > 0.05$; Table 2). Besides, ROIs were extracted and compared between the groups. Total volumes of all described regions were observed to be statistically similar between SA and C80 groups ($p > 0.05$, Table 1 Supplementary data).

Table 2. Whole-brain and regional metabolic activities across the groups.

	SA	**C80**	**C50**	**AD**	**SA vs. C80 p-values**
FDG-SUVr					
Whole-brain cortical uptake	1.03 (±0.06)	0.97 (±0.04)	1.07 (±0.06)	0.9 (±0.03)	0.18
Right ACC	0.89 (±0.14)	0.89 (±0.08)	1.04 (±0.10)	0.85 (±0.08)	0.99
Left ACC	0.87 (±0.14)	0.88 (±0.12)	1.00 (±0.09)	0.87 (±0.07)	0.98
Right PCC	1.19 (±0.21)	1.16 (±0.14)	1.29 (±0.11)	0.96 (±0.10)	0.95
Left PCC	1.18 (±0.21)	1.15 (±0.10)	1.28 (±0.12)	0.95 (±0.09)	0.97
Right pACC	1.02 (±0.08)	0.88 (±0.07)	1.12 (±0.14)	0.86 (±0.08)	0.01*
Left pACC	1.04 (±0.09)	0.93 (±0.08)	1.17 (±0.10)	0.89 (±0.09)	0.04*
Right sACC	0.97 (±0.08)	0.83 (±0.06)	1.05 (±0.12)	0.80 (±0.10)	0.009*
Left sACC	0.99 (±0.08)	0.85 (±0.05)	1.06 (±0.09)	0.81 (±0.09)	**0.003****
Right vACC	0.99 (±0.07)	0.85 (±0.06)	1.08 (±0.13)	1.72 (±0.56)	0.006*
Left vACC	1.02 (±0.08)	0.89 (±0.06)	1.12 (±0.09)	1.80 (±0.60)	0.007*
Right Hippocampus	0.92 (±0.04)	0.81 (±0.06)	0.96 (±0.05)	0.71 (±0.1)	0.006*
Left Hippocampus	0.91 (±0.05)	0.81 (±0.06)	0.97 (±0.06)	0.65 (±0.09)	0.01*

*p-values<0.05 uncorrected; **p-values <0.05 after corrected for multiple comparisons. ACC – Anterior Cingulate Cortex. sACC – Subgenual ACC. pACC – Presubgenual ACC. vACC – Ventral ACC.

Left sACC FDG SUVr further showed a moderate correlation with delayed-recall memory scores for the whole sample ($r = 0.41$, $p < 0.05$; BCa 95% CI: r = 0.12:0.62) and for older adults when grouped (SA and C80 groups, $r = 0.48$, $p < 0.05$; BCa 95% CI: r = 0.05:0.67) (Fig. 2a). The effect size of this relation was also found to be strong (Cohen's $d = 3.97$). Right pACC FDG SUVr revealed a moderate interaction with delayed-recall memory scores for the whole sample ($r = 0.59$, $p = 0.0006$; BCa 95% CI: r = 0.3:0.76), and even stronger interaction for the group of older adults (SA and C80 groups, $r = 0.71$, $p < 0.0001$; BCa 95% CI: r = 0.38:0.9). A regression model was employed and revealed a strong relationship between right pACC FDG SUVr and delayed-recall scores ($p = 0.03$) in a model that also accounted for volume and age (overall model R-squared = 0.63, $p < 0.001$). Though right vACC FDG SUVr exhibited a moderate correlation with delayed-recall memory scores for the entire sample ($r = 0.55$, $p = 0.001$; BCa 95% CI: r = 0.22:0.73); however, it depicted a stronger interaction for the group of older adults (SA and C80 groups, $r = 0.68$, $p = 0.0002$; BCa 95% CI: r = 0.45:0.78). Right vACC FDG SUVr also showed a significantly positive correlation with the sum of 5 scores of the RAVLT ($r = 0.65$, $p < 0.0001$; BCa 95% CI: r = 0.46:0.79), which is usually associated with learning process. After adjustments were made for age and volume, the model showed a significant association between right vACC FDG SUVr and both, delayed-recall scores (overall model R-squared = 0.60, $p < 0.0001$) and learning scores (overall model R-squared = 0.66, $p < 0.0001$).

A moderate correlation was found between both, right and left hippocampal FDG SUVr and the delayed-recall memory scores in the entire sample ($r = 0.46$ and $r = 0.47$, $p = 0.01$ and $p = 0.009$, respectively) (Fig. 2c). When calculated for each group, the correlations did not reach statistical significance for SA ($r = –0.34$), C50 ($r = 0.35$) or C80 ($r = –0.36$) groups ($p > 0.05$ for all measures). Though the model exhibited statistical significance (overall model R-squared = 0.39, $p < 0.005$), there was no association between right ($p = 0.09$) or left ($p = 0.09$) hippocampal FDG SUVr in regression models with delayed-recall memory scores when accounted for region volume and age. However, an association between right hippocampal FDG SUVr ($p = 0.04$) and learning scores was established (overall R-squared = 0.49, $p = 0.0004$).

A negative correlation between right hippocampal FDG SUVr and age in the whole sample was detected ($r = –0.57$, $p = 0.001$; BCa 95% CI: r = –0.75: –0.31), whereas, the SA group alone showed a

significantly positive relationship with age (r = 0.66, p = 0.03; BCa 95% CI: r = –0.24:0.9). The effect size of this relationship was found to be large for the complete sample (Cohen's d = 8.35) and very large for the SA group alone (Cohen's d = 45.65).

Figure 2. Correlation analysis between ROIs of FDG-PET and, cognitive scores and age. The relation between (a) left sACC FDG SUVr and delayed-recall memory scores, (b) right pACC FDG SUVr and delayed-recall memory scores, (c) right hippocampal FDG SUVr and delayed-recall memory scores. The dashed line represents the whole sample, except the AD group (black dots); while the solid lines represent group tendencies. sACC – subgenual anterior cingulate cortex. pACC – presubgenual anterior cingulate cortex. SUVr – Standardized Uptake Value ratio. SA – SuperAgers. C50 – Middle-aged controls. C80 – Age-matched controls. AD – Alzheimer's disease.

Amyloid deposition

No significant differences were observed in the AD-signature ROI composite for PIB SUVr between SA and C80 (1.25 ±0.24 vs. 1.32 ±0.25, p = 0.56) and in proportions of PIB positivity (30% SA vs. 30% C80 were PIB positive). Whole-brain PIB SUVr was observed to be correlated significantly with age in the entire sample (r = 0.51, p = 0.003; BCa 95% CI: r = 0.29:0.68), but did not reach statistical significance when calculated within groups (p > 0.05 for all groups). The relationship between whole-brain PIB SUVr and age also showed a large effect size (Cohen's d = 8.29). The regional analysis revealed no statistically significant differences between groups in any of the previously described ROIs (p > 0.05 for all ROIs, Supplementary Table 1).

3.3. MRI results

Functional connectivity

The seed-based analysis revealed decreased connectivity between left sACC gyrus and left posterior cingulate cortex in the SA group as compared to that in the C80 group (cluster size = 1286 μL, p <

0.005, uncorrected; Fig. 3a). The cluster in the posterior cingulate cortex had a volume of 1286 μL and its peak coordinates were x=14.0, y=63.5, and z=4.0. After correction for multiple comparisons, a tendency of decreased functional connectivity was noted between the described regions in the SA group as compared to that in the C80 group.

Figure 3. Seed-based functional connectivity. Decreased functional connectivity between left subgenual ACC region [in red–(a)] and left posterior cingulate cortex [in blue–(b)] in the SA group as compared to that in the C80 group. (c) Z-scores for the correlation between the left subgenual ACC seed and the cluster in the left posterior cingulate cortex in each group. SA – SuperAgers. C50 – Middle-aged controls. C80 – Age-matched controls. AD – Alzheimer's disease.

ICA showed one component that significantly distinguished SA from the C80 group (IC–6), which involved abnormal functional connectivity of both medial, superior temporal, posterior cingulate and anterior cingulate areas (Fig. 4a). This network was similar to the Papez circuit. An increased functional connectivity of right superior frontal gyrus with the IC–6 (cluster size = 1414 μL, $p < 0.005$, uncorrected) was found for the SA group in comparison to the C80 group (Fig. 4b). A significant relationship ($F = 9.464$, $p < 0.005$ uncorrected) was also observed between left medial frontal gyrus in the IC–6 and the delayed-recall memory scores in the study sample, validated by a significant Pearson's coefficient ($r = 0.7$, $p < 0.001$; BCa 95% CI: r = 0.46:0.83) (Fig. 4c). The AD group was not included in the ICA because it would bias the functional connectivity network analysis of other groups.

Figure 4. Independent component analysis of resting-state fMRI. (a) Identification of the Independent Component – 6 (Z-score = 4.033). (b) Independent component analysis showing right superior frontal gyrus, region within the IC–6 that distinguished SA from C80. (c) Regression analysis between delayed-recall memory scores and loading factors of IC–6 showing the right medial frontal gyrus and

Pearson's coefficient calculated between right medial frontal gyrus connectivity and the delayed-recall memory scores. SA – SuperAgers. C50 – Middle-aged controls. C80 – Age-matched controls. AD – Alzheimer's disease.

Cortical thickness and volume

Structural brain analysis did not reveal any difference between SA and C80 groups, when comparing cortical thickness and volume, after performing Monte-Carlo Z-null simulation correction. No statistically significant differences were found between total intracranial volume and bilateral mean cortical thickness between the SA and Control groups after correcting for multiple comparisons ($p > 0.05$, Monte Carlo Z-null simulation). However, a significant correlation between delayed-recall scores and the volume of the right hippocampus ($r = 0.38$, $p = 0.03$), though not with the left hippocampus ($p = 0.18$), was observed in the sample.

4. **Discussion**

A group of older adults with exceptional memory was identified and multimodal features of their brain areas supporting excellent memory function were examined. Selecting individuals with exceptionally high memory performance at an advanced stage of life may provide important biomarkers for memory maintenance through the aging process. The three main findings of this study were as follows: **Firstly**, SA showed subregions of anterior cingulate associated with brain activity similar to that of the middle-aged participants. **Secondly**, SA exhibited similar amyloid burden as their age-matched counterparts. **Thirdly**, in both hypothesis-driven and data-driven models of FC, SA presented altered functional connectivity in the frontal regions.

Measuring total years of education is very common, though it is a limited proxy of cognitive reserve in older adults. In contrast to the other studies on high-performing older adults, the cohort of SuperAgers in this study did not show a high level of education (Cook et al., 2017; Dekhtyar et al., 2017; Harrison et al., 2012). SuperAgers also showed a similar level of education as that of the normal agers, which eludes the assumption of increased cognitive reserve in this group.

Subregions of ACC were found to be associated with memory scores, independent of age and region volume, showing an even stronger association in SuperAgers. Specifically, the subgenual ACC area is a potential biomarker for memory maintenance in older adults. This region showed reciprocal connectivity with the hippocampus and many cortical and subcortical areas (Ongur, 2000). Though ACC is highly associated with regulation of emotions (Dunlop and Mayberg, 2014), there is growing evidence that this region is crucial for memory encoding (Schlichting and Preston, 2016) and remote memory retrieval (Ezzyat et al., 2018; Takashima et al., 2006). SuperAgers rely on higher brain activity in this region as compared to the normal agers, thereby supporting its significant relation with episodic memory performance. Furthermore, this region has a brain activity that is statistically similar to the middle-aged adults, indicating its uniqueness and youthfulness in high memory scores in older adults. It was hypothesized that both hippocampi and ventromedial prefrontal cortex are involved in memory consolidation differently. Over time, a decreased hippocampal activity and increased prelimbic prefrontal activity was noted during a remote memory retrieval task (Takashima et al., 2006). Also, sACC provides different representational aspects of memory to hippocampus, thus supporting prospective coding of information (Ezzyat et al., 2018; Guise and Shapiro, 2017). SuperAgers may present with a better memory differentiation than the normal agers, which ultimately improves memory consolidation.

Amyloid deposition in SuperAgers was similar to that of the normal agers, in this study. Recent studies on high-performing older adults presented inconsistent findings (Dekhtyar et al., 2017; Gefen et al., 2014; Lin et al., 2017), possibly due to high heterogeneity in the selection of the sample. Findings of this study are similar to those of previous studies on high-performing older adults (Dekhtyar et al., 2017), though the cohort included here are individuals of a higher age range only. Age threshold is important in the context of Alzheimer's disease because of increased amyloid deposition rate seen in the non-demented older adults as they age (Jansen et al., 2015), substantiated by a positive correlation between age and amyloid burden in this study sample. Despite showing similar regional amyloid burden as their counterparts, SuperAgers exhibited preserved brain activity in frontal areas. This highlights a possible mechanism of better coping with brain pathology, specifically in SuperAgers' brain as compared to that of cognitively normal older adults (Nyberg et

al., 2012). A recent investigation indicated that an important dose-response effect reflects the association between amyloid burden and cognitive decline (Farrell et al., 2017), which suggests that the rate of accumulation is a better predictor of cognitive decline than a single threshold. Besides, it is known that cognitive decline is strongly associated with Tau deposition (Aschenbrenner et al., 2018; Braak et al., 2006; Schilling et al., 2016). Hence, further studies assessing longitudinal amyloid and tau deposition in SuperAgers may help elucidate this mechanism.

Reduced global functional connectivity is expected with aging, though some regions are more susceptible to age-related functional changes than the others (Dennis and Thompson, 2014). A decreased functional connectivity between left sACC and PCC was detected in SuperAgers as compared to that in the C80 group, which corroborates previous findings of decreased PCC and ACC functional connectivity in high performing adults (Lee et al., 2016). Compensatory local connectivity in older adults has been previously described in many models of cognitive aging (Cabeza et al., 2002; Davis et al., 2008; Park and Reuter-Lorenz, 2009). In general, these models try to elucidate age-related changes in brain connectivity, associated with an unexpected increase in regional connectivity. However, compensatory connectivity may actually be associated with less efficient networks in older adults (Morcom and Henson, 2018). Therefore, these compensatory shifts may not necessarily occur in a preserved brain architecture. SuperAgers also exhibited increased functional connectivity in frontal regions of the IC–6, a neural network involving hippocampal and anterior cingulate regions, similar to the Papez circuit (Papez, 1937). This network showed an increase in FC of right superior frontal gyrus in the SA group as compared to that of healthy older adults and middle-aged adults. Also, right medial frontal gyrus was significantly associated with episodic memory scores. Together, these findings suggest that frontal networks have increased connectivity in the Superaging process.

This study corroborates to the role of frontal areas in maintaining a more youthful memory ability in older adults. Preserved brain features observed in this study provide evidence for the theory of brain maintenance (Nyberg et al., 2012), as SuperAgers presented metabolic and functional brain features that were statistically similar to those of the younger group. The similarity of glucose metabolism between SuperAgers and middle-aged participants in left sACC indicates the avoidance of age-related hypometabolism typically seen in cognitively normal older adults (Knopman et al., 2014; Pardo et al.,

2007). Frontal preservation was highlighted as fundamental in the preservation of memory functions during the aging process (Vidal-Piñeiro et al., 2018), which corroborates our findings. Besides, Dekhtyar et al. (2017) showed that executive functions, typically associated with the frontal activity, are maintained in high-performing older adults as compared to that in the normal performers.

Even though this study included small sample size, it is important to mention that the participants were selected through a very strict inclusion criterion of advanced age and exceptionally high cognitive scores. The sample size has been accounted as an important limitation as some outcomes did not survive the correction for multiple comparisons; thus, interpretation of the results should be carefully addressed. Even though the Apolipoprotein E (ApoE) status was unavailable for this sample, individuals without any type of family history of dementia or cognitive impairment were selected. Besides, a population-based study (Petersen et al., 2016) corroborated that PIB positivity is associated with cognitive decline, independent of APOE status. A longitudinal approach to this population is decisive to confirm whether all the described brain features are persistent or temporary. Further work is warranted to clarify the mechanisms of memory maintenance in a longitudinal and multimodal brain analysis.

Overall, these results authenticate the key role of anterior cingulate cortex in the exceptional memory ability of SuperAgers, even in the presence of amyloid deposition. Metabolic and functional changes of the subgenual and pre-subgenual areas may be essential in maintaining high memory performance in older adults. In particular, subgenual ACC is a potential biomarker of memory function in older adults.

Acknowledgements: WVB, ELC and GR received a CAPES scholarship (PBE-DPM II, Programa de Excelência Acadêmica and PDES, respectively). JCC is funded by CNPq (Bolsa de produtividade de pesquisa). We would like to thank Luciana Borges Ferreira for support in the data acquisition of this study.

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Declaration of interests: None.

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***Verification**

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Declaration of interests: None.

Data presented in this study have not been previously submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

All authors have reviewed and approved this manuscript in its final version. They approve the submission of this content and they validate the accuracy of this data.

FIG1
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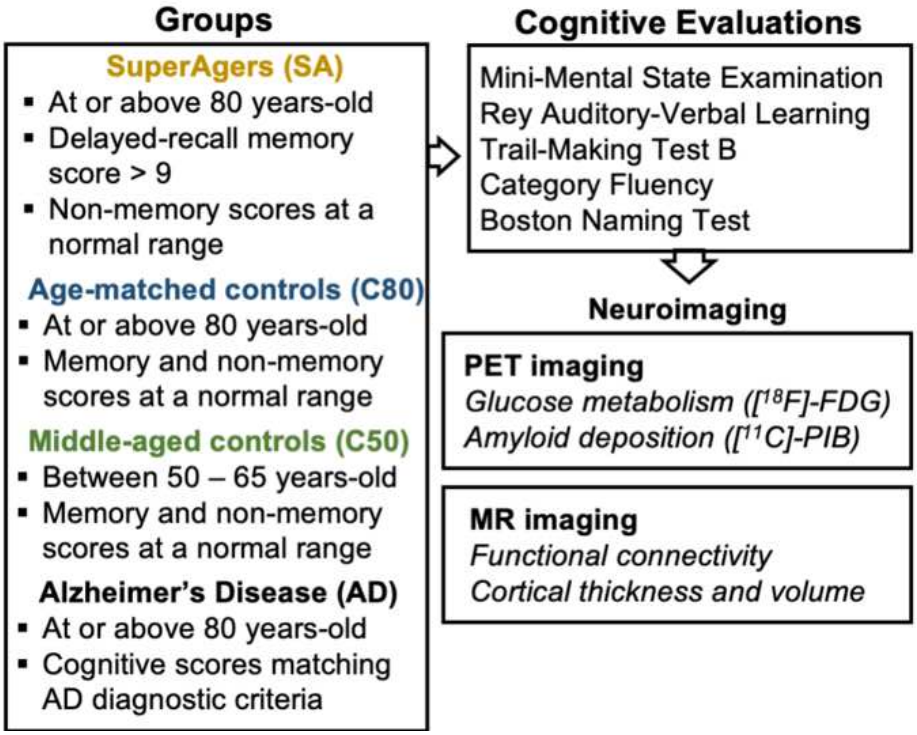

FIG2
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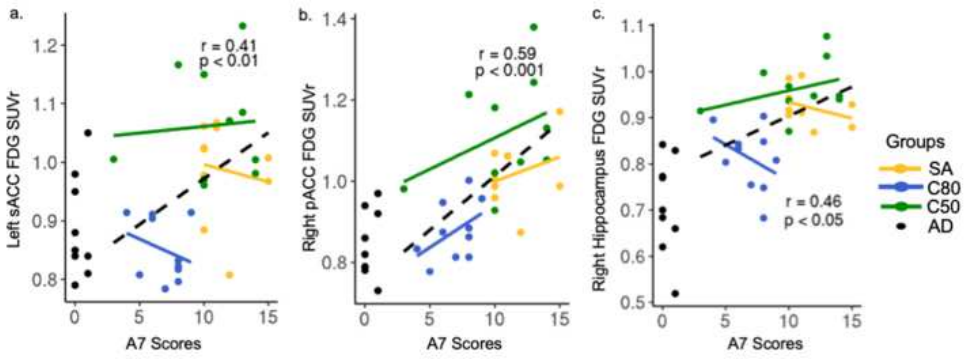

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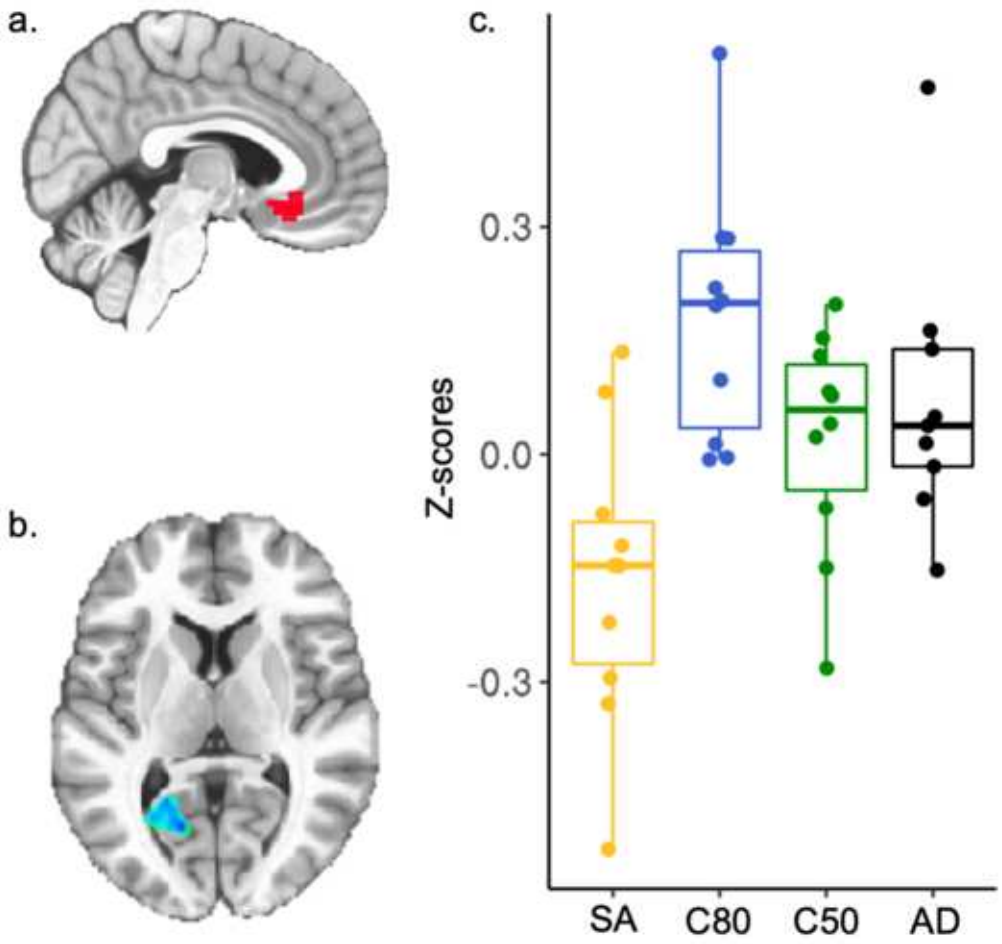

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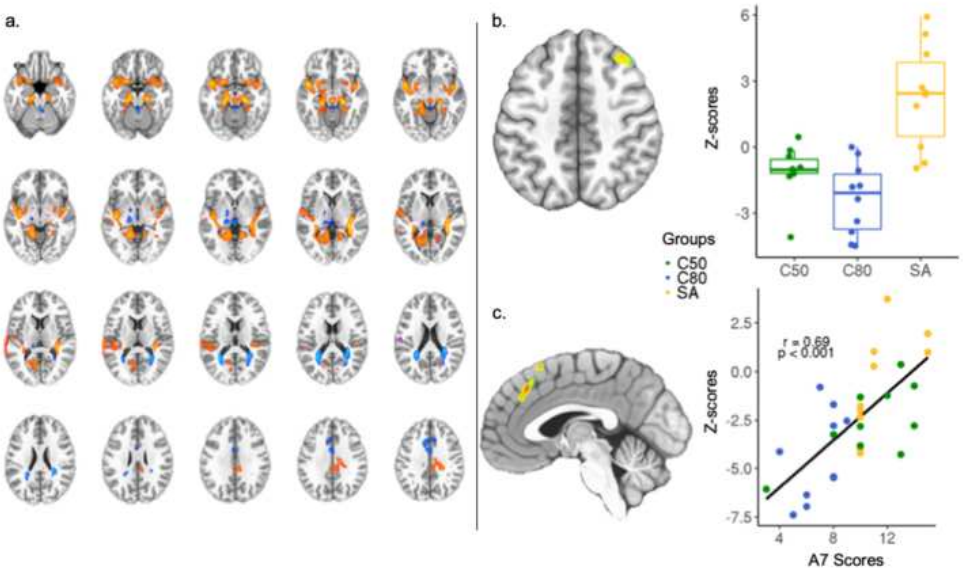
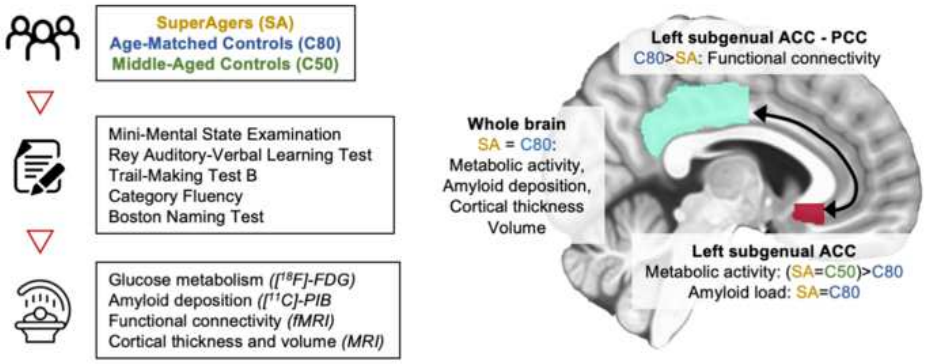


Graphical Abstract (for review)



Estudo 4. Conectividade cerebral compensatória em Superidosos: uma Joint-ICA de rs-fMRI e FDG-PET.

Esse estudo foi submetido e aceito para apresentação no 25th Annual Meeting of the Organization for Human Brain Mapping.

Compensatory brain connectivity in SuperAgers: a Joint-ICA of rs-fMRI and FDG-PET

Presented During: Poster Session
Tuesday, June 11, 2019: 12:45 PM - 02:45 PM

Poster No:

T414

Submission Type:

Abstract Submission

Authors:

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Institutions:

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Introduction:

Multimodal imaging with MRI and PET provides unique features of brain networking and functionality. For functional MRI, independent component analysis (ICA) has been increasingly used to its robustness to artifacts and low false-positive ratio. However, ICA can also be used to analyze joint variance of multimodal imaging data[1]. Herein, we investigated joint features of metabolic activity and functional connectivity in subjects that are considered SuperAgers[2] compared to age-matched controls.

Methods:

Ten SuperAgers (SA, 7 females, mean age = 82.1 years-old; SD = 2.5; range = 80-91) and ten healthy, community-dwelling older adults (Controls, 7 females, mean age = 83.8 years-old; SD = 3.7; range = 80- 91) underwent a clinical and cognitive examination followed by an MRI and PET imaging session with the radiotracer 18F-FDG. Criteria for inclusion in the SA group was defined as 80 years or more and a Delayed-Recall Memory Score (RAVLT, A7 list)[2] similar to that of individuals 50-60 years of age. Control group participants were 80 years or more and cognitively average for their age. Any medical history of neurologic or psychiatric conditions were considered exclusion criteria and all patients gave a written consent for this study. PET-FDG dynamic images and MRI data acquisition and processing steps followed international guidelines (ADNI) using the AFNI software [3]. FDG-PET preprocessing steps involved averaging from 30 to 60 minutes post-injection image, motion correction, coregistration to the subject MRI space and subsequently to the MNI152 space. Voxel-wise Standardized Uptake Value Ratios (SUVR) were calculated for FDG-PET images using cerebellum grey matter as a reference.

Resting-state fMRI data was collected on a GE Signa HDxt with a TR of 2s, a duration 7 minutes, and with 29 slices. FMRI preprocessing steps were performed for motion correction, despiking, slice time correction, scaling and registration to the MNI152 space. Regional Homogeneity (ReHo) was calculated for the BOLD time series data in each voxel and its 27 nearest contiguous voxels.
Unimodal statistical analysis was performed with independent sample t-tests and a threshold of $p< 0.005$ and a minimum cluster size of 1.286 mL. Ten independent components were estimated by the fusion of ReHo and FDG-PET connectivity networks with joint independent component analysis (J-ICA) using the FIT toolbox (v2.0, MIALAB) for MATLAB, according to previously published protocol[4]. Loading factors where compared across groups for each component. P-values<0.005 were considered significant. Data is showed in mean ± standard deviation.

Results:

SuperAgers showed an increased FDG SUVR in the right posterior cingulate region (2.401mL, $p<0.005$), right cuneus (1.647mL, $p<0.005$), left middle occipital gyrus (1.647mL voxels, $p<0.005$), right middle frontal gyrus (1.414mL, $p<0.005$) and right inferior frontal gyrus (1372mL, $p<0.005$) compared with normal controls (Fig 1). Unimodal ReHo analysis didn't show any significant statistical difference between groups. The fusion model produced one important joint component (IC6) in which the loading factors distinguished SA from Controls (0.15±0.04 vs. 0.10±0.03, $p<0.005$). The IC6 (Fig 2) revealed increased FDG SUVR in both lingual gyri and right middle occipital gyrus associated with decreased ReHo in the same regions but also increased connectivity in the left dorsolateral prefrontal cortex and right superior frontal gyrus.

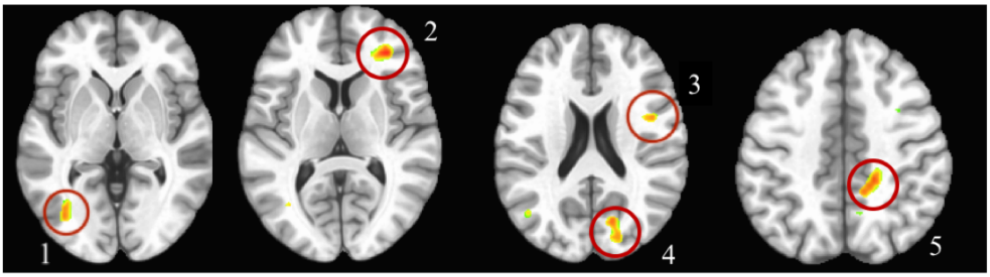

Figure 1. Unimodal voxelwise different regions of FDG-PET contrasting SuperAgers vs. Controls ($p<0.005$). 1. Left middle occipital gyrus; 2. Right middle frontal gyrus; 3. Right cuneus; 4. Right inferior frontal gyrus; 5. Posterior cingulate gyrus.

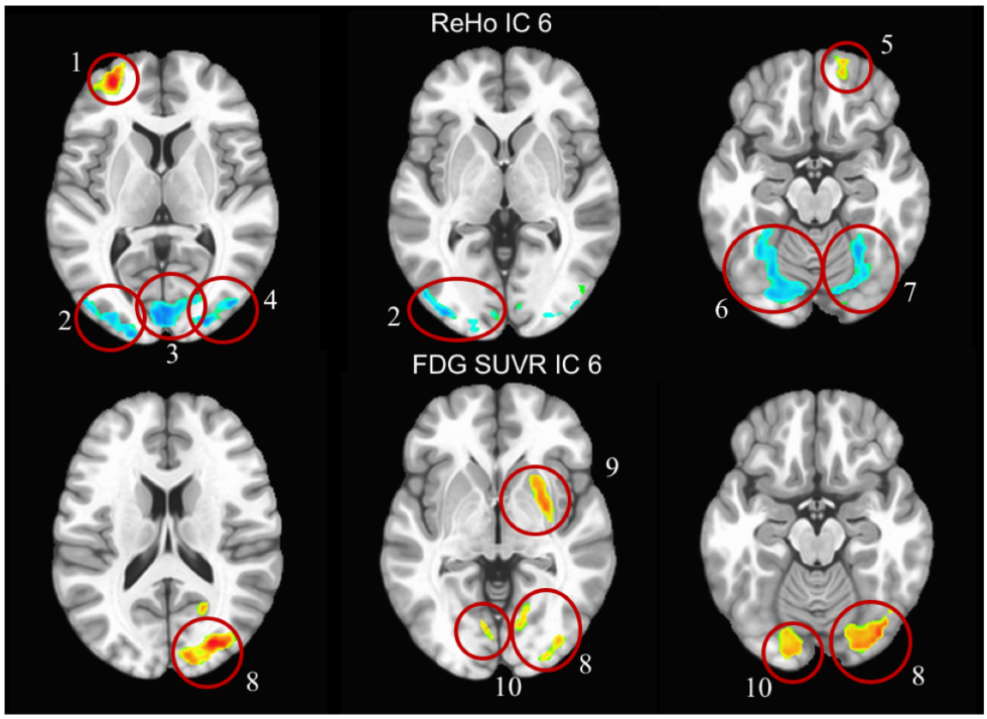

Figure 2. J-ICA of Regional Homogeneity and FDG-PET, Independent component 6, for SuperAgers and Controls (p<0.005). 1. Left middle frontal gyrus; 2. Left middle occipital gyrus; 3. Left cuneus; 4. Right middle occipital gyrus; 5. Right superior frontal gyrus; 6. Left lingual gyrus; 7. Right lingual gyrus. 8. Right lingual gyrus, right middle occipital gyrus and right cuneus; 9. Right lentiform nucleus; 10. Left lingual gyrus.

Conclusions:

J-ICA revealed additional brain differences that were not found in a unimodal analysis. The J-ICA analysis revealed that SuperAgers showed an increased association between a higher metabolic rate in the lingual gyri and posterior occipital areas and lower functional connectivity in the same region, but increased activity in frontal regions. These findings suggest that complex cerebral changes of SuperAgers may lead to a compensatory posterior-anterior shift in brain connectivity.

Higher Cognitive Functions:

Higher Cognitive Functions Other

Imaging Methods:

BOLD fMRI
PET

Lifespan Development:

Aging [1]

Modeling and Analysis Methods:

Multivariate modeling [2]

Keywords:

Aging
FUNCTIONAL MRI
Memory
Multivariate
Positron Emission Tomography (PET)

[1|2]Indicates the priority used for review

My abstract is being submitted as a Software Demonstration.

No

Please indicate below if your study was a "resting state" or "task-activation" study.

Resting state

Healthy subjects only or patients (note that patient studies may also involve healthy subjects):

Healthy subjects

Was any human subjects research approved by the relevant Institutional Review Board or ethics panel? NOTE: Any human subjects studies without IRB approval will be automatically rejected.

Yes

Was any animal research approved by the relevant IACUC or other animal research panel? NOTE: Any animal studies without IACUC approval will be automatically rejected.

Not applicable

Please indicate which methods were used in your research:

PET
Functional MRI
Neuropsychological testing

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

AFNI
Other, Please list

Provide references using author date format

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PARTE III

6 CONCLUSÃO

Este trabalho se propôs à análise de neuroimagem multimodal de Superidosos através de PET-FDG, PET-PIB, RMf e RMe. Primeiramente, foi realizada uma revisão sistemática de literatura para identificação do conhecimento atual acerca das características cerebrais de SI, seguido de uma definição operacionalizada para o contexto brasileiro. Posteriormente, é apresentado o estudo resultante da coleta de dados de neuroimagem de Superidosos correspondente à metodologia desta tese, e por último a análise de neuroimagem multimodal deste grupo.

A busca pela assinatura neurobiológica de Superidosos iniciou na coleta de dados já existentes com a revisão sistemática. Nessa revisão foram identificados achados estruturais e moleculares relacionados aos SI. Os artigos sugerem menor atrofia cortical, porém não relacionada com tamanho ou contagem total de neurônios desse grupo. Idosos de alta performance mostraram mesmo depósito amiloide quando comparado com idosos normais para a idade; no entanto, aqueles idosos de alta performance que mantiveram o escore após três anos tiveram menos acúmulo amiloide, de acordo com a literatura. No entanto, diversos estudos foram excluídos da análise por não apresentarem critérios de inclusão adequados para o estudo de idosos de alta performance.

Nesse âmbito, foi criada uma definição operacionalizada com finalidade de facilitar estudos posteriores na identificação de idosos de alta performance. Para isso, o contexto sociocultural e demográfico (como expectativa de vida) devem ser levados em conta, assim como a disponibilidade de escores cognitivos com tabelas normatizadas para idosos analfabetos. Portanto, os critérios de idade, escores cognitivos de memória e de não-memória devem ser cuidadosamente selecionados. É proposto que idosos de alta performance tem como idade mínima 75 anos, com escores de memória episódica (visual ou verbal) similares a indivíduos de 50-65 anos e escores de outras funções normais para a idade, medidos por testes cognitivos globais (como o Addenbrooke's Cognitive Evaluation).

Dentro desta definição encontram-se os Superidosos, estudados empiricamente no terceiro estudo. A área subgenual esquerda do Cíngulo Anterior apresentou aumento de metabolismo de glicose apenas no grupo SI quando comparado com o grupo de idosos normais para a idade, sendo similar ao grupo de indivíduos de meia-idade. Além disso, a atividade metabólica de subgenual esquerda e presubgenual direita mostraram importantes associações com escores de memória na amostra. A conectividade funcional de SI foi diminuída entre a parte subgenual esquerda do cíngulo anterior e o cíngulo posterior em relação aos idosos normais para a idade,

sugerindo que SI não possuem a alteração de conectividade compensatória esperada com o envelhecimento. Além disso, no modelo de Análise de Componentes Independentes, a rede IC-6 mostrou maior conectividade para o grupo SI no giro frontal superior direito em relação a idosos normais para a idade. Esse componente demostrou forte associação do giro frontal medial direito com escores de memória episódica, corroborando a importância de redes frontais na manutenção de memória em Superidosos. No entanto, a espessura cortical e volumetria cortical global e do cíngulo anterior não demonstraram diferenças entre SI e idosos normais para a idade, possivelmente devido ao pequeno tamanho amostral.

Por fim, a fusão dos métodos PET-FDG e RMf possibilitaram uma nova abordagem no estudo de SI. Através da J-ICA, foi demonstrado que os SI apresentam uma associação maior entre hipermetabolismo posterior e menor conectividade posterior, mas maior conectividade frontal. Esse desacoplamento metabólico-funcional sugere que áreas posteriores, apesar de demonstrarem maior atividade metabólica, tem conectividade deslocada para áreas frontais. Esse modelo corrobora a alteração para atividade frontal demonstrada no estudo unimodal.

Em suma, os Superidosos parecem apresentar atividade cerebral frontal correspondente à hipótese de manutenção cerebral, proposta por Nyberg (2012). Mesmo na presença de patologia amiloide, esse grupo apresenta atividade metabólica e funcional frontal maior que idosos normais para a idade. Em especial, a área subgenual esquerda do cíngulo anterior, o giro frontal medial direito e o giro frontal superior direito apresentaram características importantes nos SI, sugerindo seus possíveis usos como biomarcadores de envelhecimento cognitivo bem-sucedido.

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ANEXOS E APÊNDICES

ANEXO A - Aprovação do projeto em Comitê de Ética

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Correlação entre neuroimagem molecular, estrutural e funcional em Superidosos

Pesquisador: Jaderson Costa da Costa
Área Temática:
Versão: 5
CAAE: 51257615.6.0000.5336
Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.608.823

Apresentação do Projeto:
O pesquisador principal do estudo: "Correlação entre neuroimagem molecular, estrutural e funcional em Superidosos" encaminhou ao CEP-PUCRS, em 01/06/2016, os seguintes documentos: "Oficio_resposta.pdf" e "TCLE_V5.pdf".

Objetivo da Pesquisa:
Analisar o padrão de deposição da placa amiloide, metabolismo de glicose, estrutura cortical e funcional do cérebro de Superidosos em relação a
idosos cognitivamente normais e indivíduos com demência de Alzheimer.

Avaliação dos Riscos e Benefícios:
Não modificados em relação a versão anterior.

Comentários e Considerações sobre a Pesquisa:
Trata-se de uma emenda de ajuste, conforme solicitação prévia do CEP.

Considerações sobre os Termos de apresentação obrigatória:
Adequados.

Recomendações:
Aprovação.

Endereço: Av.Ipiranga, 6681, prédio 50, sala 703
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3320-3345 **Fax:** (51)3320-3345 **E-mail:** cep@pucrs.br

ANEXO B - Termo de consentimento livre e esclarecido

Estamos convidando o Sr. (a) / seu familiar a participar de uma nova pesquisa sobre envelhecimento. Este termo de consentimento diz respeito a uma pesquisa sobre idosos de vários níveis de inteligência que está sendo realizada no Instituto do Cérebro do Rio Grande do Sul.

O participante do estudo está sendo convidado porque possui Doença de Alzheimer, ou inteligência acima da média, ou é um indivíduo com inteligência normal. Antes de participar deste estudo, gostaríamos que você conhecesse o que ele envolve.

Este será o primeiro estudo brasileiro que avaliará pessoas com mais de 50 anos e idosos com inteligência acima da média para a idade. Iremos dividir os pacientes em grupos para avaliar as diferenças e semelhanças entre cérebros de pessoas com diferentes níveis de inteligência. Todos os grupos serão seguidos e tratados de forma igual até o fim do estudo.

O objetivo desse estudo é avaliar os cérebros de diversas pessoas com diferentes níveis de inteligência a fim de investigar potenciais alvos terapêuticos, possíveis causas e avançar no conhecimento dessa doença cada vez mais comum. Além disso, procuramos também relacionar o cérebro de pacientes com inteligência acima da média, buscando semelhanças e diferenças com os indivíduos dos outros grupos.

1. TÍTULO DA PESQUISA: **"Correlação entre neuroimagem molecular, estrutural e funcional em Superidosos",** sob a responsabilidade do pesquisador Dr. Jaderson Costa da Costa.

2. AVALIAÇÃO DO RISCO DA PESQUISA:
   ( ) RISCO MÍNIMO ( ) RISCO MÉDIO
   (X) RISCO BAIXO ( ) RISCO MAIOR

3. DURAÇÃO DA PESQUISA: 3 anos.

SEQUÊNCIA DE PROCEDIMENTOS A SEREM REALIZADOS NA PESQUISA:

1 - Consulta com um neurologista, para exame médico neurológico completo.

2 - Consulta com um neuropsicólogo ou assistente, para estimar o nível de inteligência.

3 - Realizará um exame de Ressonância Magnética, seguida de um exame de PET/CT, no Instituto do Cérebro, em dois dias seguidos. No primeiro dia, serão realizados um exame de Ressonância e um PET/CT. No outro dia, serão realizados outra Ressonância e outro PET/CT.

DESCRIÇÃO DOS PROCEDIMENTOS REALIZADOS:

A consulta médica terá em vistas a história médica completa do participante do estudo, em busca de qualquer doença existente, também sendo realizado um exame neurológico. A consulta neuropsicológica terá testes neuropsicológicos, que são uma série de perguntas e figuras que estimam a inteligência, para então dividir em grupos e continuar com os exames de imagem.

Para o exame de ressonância magnética o participante do estudo será colocado em uma maca e movido lentamente para dentro do aparelho de ressonância magnética ("aparelho em forma de tubo") e permanecerá em torno de 30 minutos, sem necessidade de nenhum procedimento invasivo, ou seja, nenhum corte, apenas a punção de uma veia quando for necessário; um alto-falante possibilita a comunicação com os pesquisadores durante todo o tempo do exame.

O procedimento PET/CT é uma tomografia computadorizada (exame de imagem) feita primeiramente com glicose marcada com Flúor-18, e em seguida com o Composto B de Pittsburgh, que são radiofármacos de meia vida muito rápida (a cada 110 minutos a atividade cai pela metade).

RISCOS E DESCONFORTOS DA PESQUISA:

São mínimas as chances de você apresentar uma reação adversa ao radiofármaco. Mas caso você tenha alguma alteração no organismo após a injeção, por favor, nos comunique.

Permanecer em jejum antes do exame.

Levar uma injeção na veia para introduzir o radiofármaco para o exame de imagem;

Ficar imóvel na máquina por 15 a 20 minutos.

O ruído do aparelho de ressonância magnética durante os primeiros 15 minutos. Iremos fornecer tapa-ouvidos para deixa-lo mais confortável.

Não existem efeitos que causem prejuízos associados com a ressonância magnética.

POSSÍVEIS BENEFÍCIOS DA PESQUISA:

Realização de exames de imagem de alta-tecnologia não disponíveis na rede pública.

Consulta neuropsicológica e avaliação neuropsicológica.

Consulta médica neurológica especializada completa.

ASSISTÊNCIA A EMERGÊNCIAS:

Em caso de qualquer problema ao participante do estudo relacionado a algum procedimento realizado durante à pesquisa, será disponibilizado atendimento médico imediato pelos médicos responsáveis pela pesquisa e será providenciado tratamento adequado, sem nenhum custo, em ambulatório especializado.

O indivíduo que tiver qualquer problema de saúde relacionado a algum procedimento realizado em relação à pesquisa terá atendimento médico imediato e será providenciado tratamento adequado, sem nenhum custo.

Caso o participante do estudo sentir-se desconfortável durante os exames, o mesmo será suspenso e o Sr. (a) / seu familiar será avaliado por médico do Instituto do Cérebro do Rio Grande do Sul. Nossa equipe realizará acompanhamento ambulatorial até a resolução completa do quadro.

PRIVACIDADE DE SIGILO:

Os resultados dos testes realizados durante a pesquisa serão sempre tratados confidencialmente ou em segredo, seu nome não irá aparecer em nenhum momento e em nenhum local. Os resultados deste estudo poderão ser publicados em um jornal científico ou submetidos, mas você não será identificado por nome.

Ressaltamos que a concordância em participar deste estudo e realizar os exames adicionais não implica necessariamente em qualquer modificação no tratamento que jê está sendo feito. A não concordância em participar deste estudo não irá alterar de nenhuma maneira o tratamento já estabelecido, e o participante do estudo poderá retirar o seu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades, prejuízo ou perda de qualquer benefício que possa ter adquirido.

DÚVIDAS E INFORMAÇÕES:

O participante do estudo pode, a qualquer momento, solicitar novas informações e modificar sua decisão se assim eu desejar. O Dr. Jaderson Costa da Costa, ou sua equipe, certifica que todos os resultados dos exames

serão confidenciais e mantidos em sigilo, e o participante do estudo terá liberdade de retirar o consentimento de participação na pesquisa, em face destas informações.

Caso tiver novas perguntas sobre este estudo, posso entrar em contato com um dos membros da equipe do estudo e chamar os seguintes médicos: Dr. Jaderson Costa da Costa pelo telefone (051) 33203000, ramal 2693; Wyllians Vendramini Borelli pelo telefone (051) 91019123; Dr. Lucas Porcello Schilling pelo telefone (051) 99531080.

Instituto do Cérebro do Rio Grande do Sul: Avenida Ipiranga, 6690 – Jardim Botânico – Porto Alegre/RS. Telefone: (51) 3320.3485.

Comitê de Ética em Pesquisa da PUCRS: Av. Ipiranga 6681, Prédio 40 – Sala 505.
Porto Alegre/ RS – Brasil – CEP: 90610-900. Telefone: (51) 3320.3345. E-mail: cep@pucrs.br

Horário de Atendimento - Atendimento pelo fone (51) 3320-3345

De segunda a sexta-feira.

Manhã: 8h30min às 12h.

Tarde: 13h30min às 17h (Expediente Interno)

COM RELAÇÃO ÀS ATRIBUIÇÕES DO COMITÊ DE ÉTICA EM PESQUISA:

O comitê de ética em pesquisa é responsável sobre pesquisas em seres humanos, em relação à ética em pesquisa, garantia de integridade e dignidade dos participantes, aprovação ou não de protocolos de pesquisa, confidencialidade das informações da pesquisa, acompanhamento e desenvolvimento dos projetos. Além disso, o comitê atua com papel consultivo e educativo, e é responsável no recebimento de denúncias, abusos e notificações gerais que alterem o curso do estudo, zelando pela proteção ao indivíduo que aceita participar do estudo. O Comitê de Ética mantém comunicação regular com o Comitê Nacional de Ética em Pesquisa (CONEP) e zela pela correta aplicação deste regulamento.

DIREITOS DOS SUJEITOS DE ESTUDOS DE PESQUISA

Concordo voluntariamente em participar desse estudo. Li (ou foi-me lido) as informações acima fornecidas. Tive a oportunidade de fazer perguntas e todas elas foram respondidas de forma satisfatória. O médico / pessoa designada e eu vamos assinar, rubricar e datar duas vias neste termo de consentimento. Vou guardar uma delas e a equipe do estudo guardará a outra em seu arquivo.

Ao assinar esse termo concordo, de livre e espontânea vontade, em participar do estudo descrito nesse termo de consentimento.

_____
NOME DO SUJEITO DE PESQUISA

_____ _____
ASSINATURA **DATA**

_____
NOME DO REPRESENTANTE LEGAL / TESTEMUNHA (SE APLICÁVEL)

_____ _____
ASSINATURA **DATA**

_____
NOME DO PESQUISADOR RESPONSÁVEL

_____ _____
ASSINATURA **DATA**

ANEXO C - Formulário de Pre-Screening Telefônico

InsCer Instituto do Cérebro

☐ Incluso

1. PRE-SCREENING TELEFÔNICO – Superidosos

Entrevistador:

1. DADOS DEMOGRÁFICOS

1.1. **Nome:** _____ **Número:** _____

1.2. **Idade:** ____

1.3. **Telefone:** ( ) _____

1.4. **Anos de escolaridade:** _____
(1° grau – 8 / 2° grau – 3) (Primário – 4/ Ginásio – 4/ Científico – 3)

1.5. **Possível grupo:** ( ) **Superidosos**
( ) **Controle Meia-Idade**
( ) **Controle Idoso**
( ) **DA**

Limitação financeira ao estudo?
☐ Estacionamento
☐ Auxílio

2. ESTADO DE SAÚDE ATUAL

1.6. **Doença neurológica:**
- ☐ **AVC**
- ☐ **Aneurisma cerebral**
- ☐ **Convulsões**
- ☐ **Parkinson**
- ☐ **Alzheimer**
- ☐ **Encefalite**

2.2 **Doença hepática:** _____

2.3 **Doença renal:** _____

2.4 **Doença autoimune:** _____

2.5 **Câncer:** _____

2.6 **Outras doenças:** _____

2.7 **MEDICAÇÕES EM USO:** _____
_____
_____

CONDIÇÕES RNM: (marcar se tiver algum)

Metal no corpo	Marca-passo	Clipe aneurisma	Implante dentário/ortodôntico	Válvula cardíaca / Cirurgia cardíaca

SCREENING MARCADO DIA: _____ **às** _____ **(duração: 2h)**

***VIR ACOMPANHADO**

***TRAZER EXAMES ANTERIORES (IMAGEM E SANGUE)**

***AVISAR SE NECESSIDADE DE ESTACIONAMENTO**

ANEXO D - Formulário de Screening Neurológico

2.1. SCREENING NEUROLÓGICO – SUPERIDOSOS

Entrevistador:

ANAMNESE

Nome: _____ **Número:** _____

Idade: ____ **Anos de escolaridade:** _____

Trabalho/ocupação:_____

HISTÓRIA MÉDICA PREGRESSA

Doença neurológica:

- ☐ **AVC**
- ☐ **Aneurisma cerebral**
- ☐ **Convulsões**
- ☐ **Parkinson**
- ☐ **Alzheimer**
- ☐ **Encefalite**

Doença hepática: _____ **Colesterol:** _____

Doença renal: _____

Doença autoimune: _____

Câncer: _____

Doença cardíaca:_____ **PA:**_____

GO:_____

TRH (qual/quant/tempo):_____

Doença psiquiátrica (Depressão / Bipolaridade / Alucinações / Psicose):_____

Outras doenças: _____

MEDICAÇÕES EM USO: _____

_____

_____

HISTÓRIA FAMILIAR

- ☐ **Doença Neurológica. Qual?** _____
- ☐ **DM (1) / (2)**
- ☐ **HAS**
- ☐ **Outra(s):** _____

EXAME FISICO

Sensibilidade: **Altura:**

Força: **Peso:**

Reflexos:

Pares cranianos:

CONDIÇÕES DA RM

Metal no corpo	Marca-passo	Clipe aneurisma	Implante dentário/ortodôntico	Válvula cardíaca / Cirurgia cardíaca

NOTAS:_____

_____

_____

_____

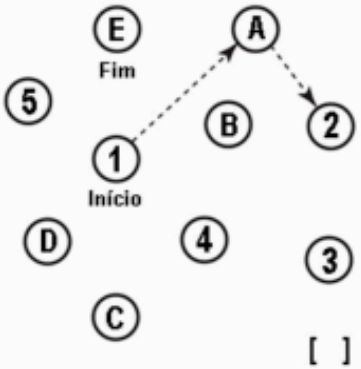
ANEXO E - Montreal Cognitive Assessment

2.2. Montreal Cognitive Assessment (MoCA)

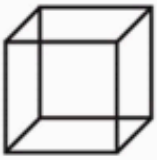
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Versão Experimental Brasileira

Nome:_____ Data de nascimento: __/__/__
Escolaridade:_____ Data de avaliação: __/__/__
Sexo:_____ Idade:_____

VISUOESPACIAL / EXECUTIVA — Pontos



Copiar o cubo



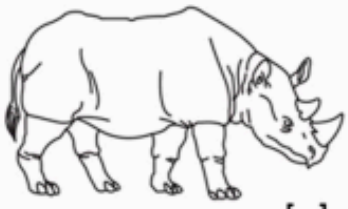
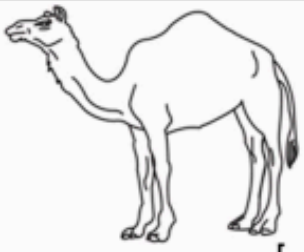
[ ] [ ]

Desenhar um RELÓGIO (onze horas e dez minutos) (3 pontos)

[ ] Contorno [ ] Números [ ] Ponteiros

__/5

NOMEAÇÃO

[ ] [ ] [ ]

__/3

MEMÓRIA — Leia a lista de palavras, O sujeito de repeti-la, faça duas tentativas. Evocar após 5 minutos

	Rosto	Veludo	Igreja	Margarida	Vermelho
1ª tentativa					
2ª tentativa					

Sem Pontuação

ATENÇÃO — Leia a seqüência de números (1 número por segundo)

O sujeito deve repetir a seqüência em ordem direta [ ] 2 1 8 5 4
O sujeito deve repetir a seqüência em ordem indireta [ ] 7 4 2

__/2

Leia a série de letras. O sujeito deve bater com a mão (na mesa) cada vez que ouvir a letra "A". Não se atribuem pontos se ≥ 2 erros.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Subtração de 7 começando pelo 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 ou 5 subtrações corretas: 3 pontos; 2 ou 3 corretas 2 pontos; 1 correta 1 ponto; 0 correta 0 ponto

__/3

LINGUAGEM — Repetir: Eu somente sei que é João quem será ajudado hoje. [ ]

O gato sempre se esconde embaixo do Sofá quando o cachorro está na sala. [ ]

__/2

Fluência verbal: dizer o maior número possível de palavras que comecem pela letra F (1 minuto). [ ]_____ (N ≥ 11 palavras)

__/1

ABSTRAÇÃO — Semelhança p. ex. entre banana e laranja = fruta [ ] trem - bicicleta [ ] relógio - régua

__/2

EVOCAÇÃO TARDIA

	Deve recordar as palavras SEM PISTAS	Rosto	Veludo	Igreja	Margarida	Vermelho	Pontuação apenas para evocação SEM PISTAS
		[ ]	[ ]	[ ]	[ ]	[ ]	
OPCIONAL	Pista de categoria						
	Pista de múltipla escolha						

__/5

ORIENTAÇÃO — [ ] Dia do mês [ ] Mês [ ] Ano [ ] Dia da semana [ ] Lugar [ ] Cidade

__/6

Versão experimental Brasileira: *Ana Luisa Rosas Sarmento*
Paulo Henrique Ferreira Bertolucci - José Roberto Wajman
(UNIFESP-SP 2007)

TOTAL
Adicionar 1 pt se ≤ 12 anos de escolaridade __/30

ANEXO F – Capa da bateria de avaliação cognitiva

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
INSTITUTO DO CÉREBRO DO RIO GRANDE DO SUL- INSCER
ESTUDO SUPERIDOSOS

AVALIAÇÃO NEUROPSICOLÓGICA

PARTICIPANTE:_____

DATA DA AVALIAÇÃO: __/__/__

DADOS DE IDENTIFICAÇÃO DO PARTICIPANTE

Avaliador:	
Data de Nascimento:	Idade:
Ocupação:	Escolaridade:
Estado civil:	Telefone:

RESULTADOS

TESTE	BRUTOS	RESULTADO REAL
1. ACE-R / MEEM		ACE-R:
2. TMT-A		
3. TMT-B		
4. REY VERBAL-Soma		
REY VERBAL-A7		
5. BNT		
6. F A S		
7. CFT		
8. GDS - 15		
9. Digit span - TOTAL		
Digit span - DIRETO		
Digit span - INVERSO		
10. Av. Funcional (Pfeffer)		

OBSERVAÇÕES

ANEXO G - Trabalhos completos aceitos em congressos

Os seguintes resumos foram aceitos em conferências nacionais e internacionais e estão separados de acordo com o ano de publicação. Um total de 14 resumos foram apresentados.

2016: 1 trabalho.

(1) Sintomas de depressão em Superidosos (DE FREITAS et al., 2016).

2017: 6 trabalhos.

(1) Superior Memory Capacity Of Superagers Is Correlated With Higher [18f]FDG Uptake In The Hippocampus (BORELLI et al., 2017a).
(2) Functional Connectivity Of The Hippocampus And Maintenance of Memory In Superagers: Preliminary Results (TRENTIN et al., 2017). Este trabalho foi premiado com o prêmio Lundbeck de Incentivo à Pesquisa.
(3) Preliminary Data From The Superagers Project (BORELLI et al., 2017b).
(4) Resilience Level and Cognitive Abilities In Superagers (MARQUES et al., 2017).
(5) Superagers' Sociodemographic and Neuropsychological Profile (FERREIRA et al., 2017).
(6) Higher Metabolic and Functional Activity in the Hippocampus of Superagers: Na MRI And PET Imaging Study (SCHILLING et al., 2017).

2018: 7 trabalhos.

(1) Episodic Memory Decline In A PIB-Positive Superager After 15-Month Follow-Up (TONDO et al., 2018).
(2) A Descriptive Analysis of Superagers' Lifestyle (SANTOS et al., 2018a).
(3) Longitudinal Episodic Memory Performance of Superagers: Preliminary Results (BORELLI et al., 2018b).
(4) Correlation of the Addenbrooke's Cognitive Examination-Revised with Different Cognitive Functions In Middle-Aged And Elderly People (SANTOS et al., 2018b).
(5) [18F]FDG-PET Prefrontal Hypometabolic Activity Observed In Older Adults Compared With middle-aged subjects (BORELLI et al., 2018c).
(6) O quão diferenciadas são as funções executivas de Superidosos? Resultados Preliminares (SANTOS et al., 2018c).

(7) Parameter estimation for kinetic modeling of 18f-FDG in positron emission tomography (PET) image (HAUSER et al., 2018).

ANEXO H – Impacto social do projeto

Por se tratar de um assunto de amplo interesse da sociedade, essa pesquisa teve impacto gerador de conhecimento para a população através de diversas palestras e reportagens em grande mídia, possíveis através de financiamento público. As entrevistas de divulgação aberta e de maior impacto são as seguintes:

1. RBS TV/G1 - Conteúdo transmitido em rede regional de televisão dia 29/03/2017 (G1, 2017).
2. Bem Estar - Reportagem transmitida em rede nacional de televisão dia 06/02/2018 (GLOBO, 2018).
3. SBT – Reportagem transmitida em rede regional de televisão dia 05/06/2018 (SBT, 2018).
4. Estadão - Reportagem publicada em jornal dia 29/07/2018 (ESTADAO, 2018).
5. Gaúcha ZH - Reportagem publicada em jornal dia 10/11/2018 (ZH, 2018).
6. Metro – Reportagem publicada em jornal dia 26/03/2019 (METRO, 2019).
7. EPOCA – Ciência tenta entender o que torna especiais os cérebros dos ‘Superidosos’. Reportagem publicada em revista dia 30/03/2019 (EPOCA, 2019).

Foram também realizadas palestras sobre envelhecimento cognitivo bem-sucedido em diversos congressos, conferências, simpósios e seminários.

Esta pesquisa contou com um objetivo pedagógico desde sua concepção. Um total de 24 alunos, 15 do curso de medicina e 9 do curso de psicologia, estiveram envolvidos direta e indiretamente em avaliações dos participantes, apresentação em seminários, processamento e análise de diferentes tipos de neuroimagem.

ANEXO I – Artigos publicados durante o período de doutoramento, mas não relacionados diretamente com o tema da tese.

Artigo anexo 1. Causas de mortalidade em encefalopatia epiléptica prematura na infância: uma revisão sistemática.

Epilepsy & Behavior 85 (2018) 32–36

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Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Causes of mortality in early infantile epileptic encephalopathy: A systematic review

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ABSTRACT

Introduction: Early infantile epileptic encephalopathy syndrome (EIEE), also known as Ohtahara syndrome, is an age-dependent epileptic encephalopathy syndrome defined by clinical features and electroencephalographic findings. Epileptic disorders with refractory seizures beginning in the neonatal period and/or early infancy have a potential risk of premature mortality, including sudden death. We aimed to identify the causes of death in EIEE and conducted a literature survey of fatal outcomes.
Methods: We performed a literature search in MEDLINE, EMBASE, and Web of Science for data from inception until September 2017. The terms "death sudden," "unexplained death," "SUDEP," "lethal," and "fatal" and the medical subject heading terms "epileptic encephalopathy," "mortality," "death," "sudden infant death syndrome," and "human" were used in the search strategy. The EIEE case report studies reporting mortality were included.
Results: The search yielded 1360 articles. After screening for titles and abstracts and removing duplicate entries, full texts of 15 articles were reviewed. After reading full texts, 11 articles met the inclusion criteria (9 articles in English and 2 in Japanese, dated from 1976 to 2015). The review comprised 38 unique cases of EIEE, 17 of which had death as an outcome. In all cases, the suppression-burst pattern on electroencephalographies (EEGs) was common. Most cases (55%) involved male infants. The mean (standard deviation [SD]) age at onset of seizure was 19.6 ± 33 days. The mean (SD) age at death was 12.9 ± 14.1 months. Most infants (58.8%) survived less than one year. The cause of death was described only in eight (47%) patients; the cause was pneumonia/respiratory illness or sudden unexpected death in epilepsy (SUDEP).
Discussion: The results show EIEE as a severe disease associated with a premature mortality, evidenced by a very young age at death. Increasing interest in the detection of new molecular bases of EIEE is leading us to a better understanding of this severe disease, but well-reported data are lacking to clarify EIEE-related causes of death.

1. Introduction

Early infantile epileptic encephalopathy (EIEE) was first described by Ohtahara as a devastating condition in infants. Also named as Ohtahara syndrome, this rare clinical entity is characterized as frequent spasms in neonates/infants associated with a suppression-burst (S-B) pattern on electroencephalography (EEG) [1–3]. The EIEE is usually described as a part of the same epileptic, age-dependent continuum of West syndrome (WS) and Lennox–Gastaut syndrome (LGS) [3]. The major causes of EIEE include structural brain abnormalities, with genetic mutations frequently in STXBP1, KCNQ2, ARX, and CDKL5, among several others, also having a massive role in the syndrome [4–6]. This rare disease has a poor prognosis. Usually described as a progressive and untreatable disease, EIEE is also associated with severe physical and cognitive disabilities and unexplained death [3]. Among several causes of death in epilepsy, sudden unexplained death in epilepsy (SUDEP) is rising. It is defined as the "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrawning death in patients with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal structural or toxicologic etiology of death" [7]. Although mortality has increased among children with epilepsy [8], so far, no clear data are available on the causes of death in EIEE. To better understand

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1525-5050/

this point, we propose a systematic and comprehensive literature review searching for EIEE outcomes.

2. Material and methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was performed [9]. The data were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10]. The review protocol was registered in the International Register of Prospective Systematic Reviews under the registration number CRD42017058801.

2.1. Database search

A literature search was performed in the MEDLINE (through PubMed), EMBASE, and Web of Science for data from inception until September 2017. The following terms and medical subject headings (MeSH) were used in the search strategy: "epileptic encephalopathy" AND "death sudden" OR "SUDEP" OR "unexplained death" OR "mortality" OR "death" OR "sudden infant death syndrome" OR "lethal" OR "fatal" AND "case control" OR "cohort analysis" OR "retrospective study" OR "epidemiologic studies" OR "observational (study or studies)" OR "longitudinal" OR "retrospective" AND "human." The detailed strategies for PubMed are given in Appendix I. The strategies for other databases are available on request. Articles published in all languages were included. The bibliography of the included articles was manually searched. Two authors (G.R. and W.B.V.) independently evaluated the titles and abstracts of all studies identified in the search based on the abovementioned terms and MeSH. Disagreements were resolved by consensus or by a third reviewer (L.P.).

2.2. Eligibility criteria

The inclusion criteria were the following: (1) case reports or case–control or cohort studies reporting mortality and (2) criteria for the diagnosis of EIEE as (a) age up to four months; (b) S-B pattern on EEGs; (c) tonic spasms, generalized seizures, hemiconvulsions, or focal motor seizures [11,12]; and (d) death as outcome with the diagnosis of EIEE.

Exclusion criteria were studies of systematic reviews, letters, and experimental studies. In addition, the studies with incomplete EIEE diagnosis criteria were excluded. Fig. 1 shows a flowchart of study selection and inclusion.

2.3. Data extraction

The databases were searched and duplicate entries were removed. Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full text of these articles and made their selection in accordance with the eligibility criteria. Data on the following were collected: the number of cases, age (days) at seizure onset, underlying pathology, outcome, and cause of death categorized as SUDEP, infective, other, or unknown. The SUDEP cases were classified as definite, probable, or possible [7].

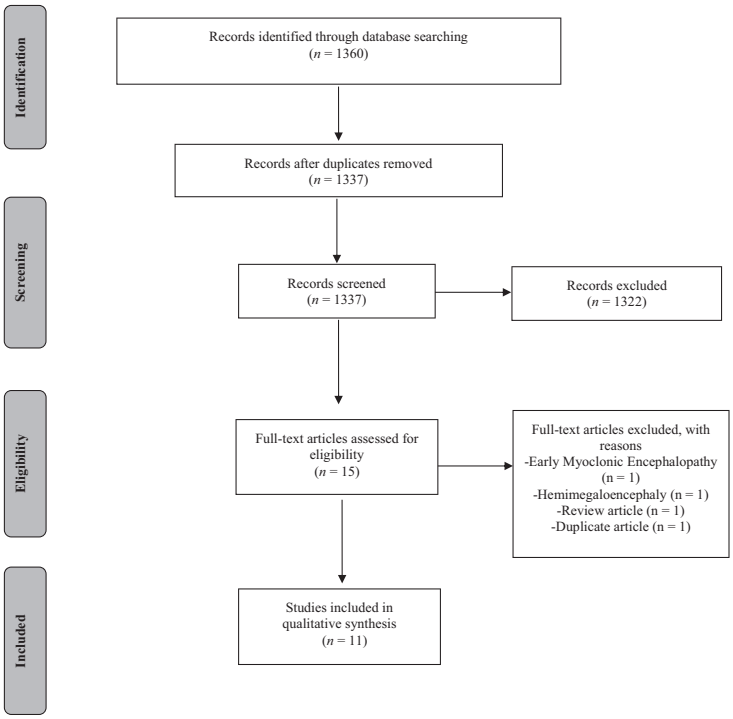

Fig. 1. Summary of evidence search and study selection.

3. Results

The search retrieved 1360 potentially relevant citations from the electronic databases. Duplicate titles were removed, leaving 1337 articles. After screening titles and abstracts, only 15 articles met the inclusion criteria; the full texts of these articles were obtained. After reading full texts, 11 articles (9 articles in English and 2 in Japanese, dated from 1976 to 2015) that met the inclusion criteria were included [1,2,13–21]. An associate researcher of the Brain Institute of Rio Grande do Sul provided a full translation of both studies in Japanese. The complete flowchart is shown in Fig. 1.

The review included 38 cases of EIEE in 10 studies (Table 1). The age at onset of seizure was from 1 to 120 days. The underlining neuronal pathology varied among cerebral atrophies, focal dysplasia, Aicardi syndrome, porencephaly, subacute encephalopathy, microcephaly, corpus callosum agenesis, and olivary dentate nuclei dysplasia. In all cases, the S-B pattern on EEGs was common. The EEG patterns varied from the resolution of waveform abnormalities to hypsarrhythmia and diffuse slow spike and wave activity. Hypsarrhythmia was the main pattern found in 16 cases. Modified hypsarrhythmia was documented in five patients. Further pathology evolution varied from LGS (5 cases) and severely handicapped patients (11 cases) to early death.

Most patients (21/38, 55%) were male infants. The mean (standard deviation [SD]) age at onset of seizure was 19.6 ± 33 days. Deaths were documented in 17 EIEE cases. The mean (SD) age at death was 12.9 ± 14.1 months. Most infants (58.8%) survived less than one year. The cause of death was described only in 8 (47%) patients; the cause was either pneumonia/respiratory illness or SUDEP. Other outcomes were excluded from this analysis, namely, progression to other epileptic syndromes (WS, LGS, spike foci) or cessation of seizures [2,13]. Four cases were described by Ohtahara as deceased after the EEG pattern turned from S-B to hypsarrhythmia. Consequently, these cases were not included in this article. Pneumonia was the cause of death in six cases (one case described as "pulmonary infection") [13,16], SUDEP in two cases, and an outcome of "respiratory illness" in one case. Of the included articles, 47% did not mention the causes of death, such as the study of Robain and Dulac [15] which only mentioned "general pathological examination was normal" without further explanation. The causes of death for the 17 cases are shown in Fig. 2.

4. Discussion

As mentioned by Ohtahara [22], EIEE can be divided into two groups, with considerably different outcomes. The typical progression of epileptic syndromes starts with an S-B pattern, followed by hypsarrhythmia and subsequently by diffuse slow spike–waves. A different group showed progression to focal spike pattern, becoming free from seizures over time.

Even with a potential group classification, unusual cases of EIEE may exist. A rising number of cases show that atypical patterns of EIEE which respond to vigabatrin may exist [23,24]. A girl had an S-B pattern on EEG that persisted until she was five years old, an atypical EIEE finding that did not follow the usual evolution of this disease [25].

The major limitation of this study is the risk of biases. Publication bias may have played a major role because researchers tend to focus on the etiologic factors of EIEE instead of outcomes. The diagnostic certainty has surely changed over time, as the included studies span almost 20 years and the definition of EIEE has now become more consistent. In addition, the clinical features of cases were poorly described, and limited supporting data were described in the literature relative to EIEE; this limits the generalization of findings.

Previously described as a main cause of death in Dravet syndrome [26], SUDEP in EIEE is poorly reported in the literature. Present results show that some children with EIEE may have died from unexplained causes. After SUDEP was clearly defined years after some of the reviewed publications, this cause of death may be underestimated as the severity of seizures is a potential factor for sudden death in infants and an S-B pattern is a key feature in EIEE. Many possible underlying causes of sudden death are suggested, mostly multifactorial from cardiac and pulmonary causes [27].

The recent development and spread of sequencing technologies have enabled the detection of several new genes involved in the pathogenic role of early-onset epileptic encephalopathies [28]. The EIEE lacks proper understanding, but identification of specific phenotype

Table 1
Summary of the patients with EIEE.

Author(s), year	Number of cases	Age (days) of seizure onset	Underlying pathology (*n*)	Outcome	Cause of death (*n*)	Death age (months)
Ohtahara et al. (1976)	8	1–86	Cerebral atrophy (2) Aicardi syndrome (1) Porencephaly (2) Subacute diffuse encephalopathy (1) Unknown (2)	Death (4) Severely handicapped (4)	Not mentioned (4)	7 11 12 19
Konno et al. (1982)	5	1–9	Cerebral atrophy (3) Unknown (2)	Death (3) LGS[a] (2)	Pulmonary infection (3)	2 4 11
Ohtahara et al. (1987)[b]	14	1–86	Cerebral atrophy (6) Aicardi syndrome (2) Porencephaly (2) Subacute diffuse encephalopathy (1) Unknown (3)	Death (4) Severely handicapped (10)	Not mentioned (4)	7 11 12 19
Clarke et al. (1987)	11	1–5	Microencephaly (4) Unknown (5)	Death (2) Severely handicapped (9)	Not mentioned (2)	1 2
Robain et al. (1992)	1	35	Olivary-dentate dysplasia	Death	Not mentioned	2
Quan et al. (2001)	1	87	Cerebral atrophy Focal cortical dysplasia	Early death	Pulmonary infection	22
Absoud et al. (2010)	1	120	ARX mutation Cerebral atrophy	Death	Not mentioned	9
Saitsu et al. (2014)	2	1–7	Unknown	Death	Pneumonia (2)	21
Vaher et al. (2014)	1	1	SCN8A mutation Bilateral frontotemporal atrophy	Death	Respiratory illness	17
Kong et al. (2015)	1	3	Unknown	Death	SUDEP[a]	16
Larsen et al. (2015)	1	120	Unknown	Death	SUDEP	60

[a] LGS, Lennox–Gastaut syndrome; SUDEP, sudden unexpected death in epilepsy.
[b] Ohtahara et al. (1987) includes the eight cases described in Ohtahara et al., 1976, written in Japanese, with the addition of 6 new cases of EIEE.

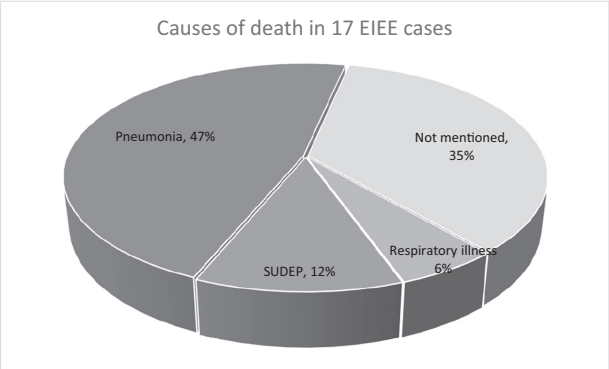

Fig. 2. Causes of death. Four categories of cause of death in 17 EIEE cases and the percentage of cases in each category.

standards associated with the discovery of molecular bases may help us provide a better diagnostic criterion for the ascending differentiation of the disease patterns [6]. Acquiring consolidated data of the outcomes of this severe disease simultaneously with the discovery of new techniques is required for further evaluation of common EIEE-related causes of death.

We encourage clinicians to share fatal cases of EIEE. The reported knowledge of EIEE is insufficient compared with that of other epileptic syndromes and therefore compromises prevention strategies and targeted therapeutics for EIEE. Understanding the major causes of mortality in EIEE is essential for family education and the control of risk factors.

5. Conclusion

This study shows EIEE as a severe disease associated with a premature mortality, evidenced by a very young age at death. Increasing interest in the detection of new molecular bases of EIEE is leading us to a better understanding of this severe disease, but well-reported data are lacking to clarify EIEE-related causes of death.

Conflict of interest

The authors have no conflicts of interest to disclose.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

MLN, FAS, and JCC are respectively 1D, 1B, and 1A researchers from CNPq – Brazil.

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Appendix I. PubMed search strategy

#1 Search Epileptic encephalopathy [MeSH Terms]
#2 Search Death sudden OR SUDEP OR unexplained death OR mortality[MeSH Terms]) OR death[MeSH Terms]) OR sudden infant death syndrome[MeSH Terms]) OR lethal OR fatal
#3 Search (Epidemiologic studies/) OR (Exp case control studies/) OR (Exp cohort studies/) OR (Case control.tw.) OR ((cohort adj (study or studies)).tw.) OR (Cohort analy$.tw.) OR ((Follow up adj (study or studies)).tw.) OR ((observational adj (study or studies)).tw.) OR (Longitudinal.tw.) OR (Retrospective.tw.)
#4 Search Human[MeSH Terms]
#5 Search (#1 AND #2 AND #3 AND #4)

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Artigo anexo 2. Função input arterial da carótida como um problema inverso em modelagem cinética do [18F]2-Fluoro-2 Deoxy-D-Glucose.

Artigo aceito para publicação na *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization,* dia 15/07/2019.

ARTICLE TEMPLATE

Carotid Arterial Input Function as an Inverse Problem in Kinetic Modeling of [18F]2-Fluoro-2 Deoxy-D-Glucose

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ARTICLE HISTORY
Compiled July 18, 2019

ABSTRACT
A two-tissue reversible compartment model is solved by Laplace transform method for kinetic modeling of [18F]2-fluor-2deoxy-D-glucose(FDG), in order to quantify amyloid in Positron Emission Tomography(PET) image. A reverse engineer technic is applied to determine the input function(Ca(t)), that represents the time-course of tracer concentration arterial blood. Ca(t) is obtained by non-linear regression, and, non-invasively from the timeactivity curve in a carotid volume of interest(VOI). After calculating a convolution integral, the analytical solution is completely described.

KEYWORDS
Laplace transform; Positron Emission Tomography(PET); kinetic modeling; image derived input function; convolution integral; nonlinear regression

1. Introduction

The image-derived arterial input function (IDAIF) provides data that are similar to arterial blood input methods and can it can be used to quantify in a non-invasive way the metabolic rate for glucose in dynamic brain [18F] 2-fluor-2deoxy-D-glucose(FDG) in positron emission tomography (PET) studies, according to previous researches (Chen et al, 1998; Dakua, 2013; Fregonara et al, 2009; Lopresti et al, 2005; Zhou, 2012).

FDG is a glucose analogue used to evaluate brain metabolic activity in vivo through positron emission tomography with computed tomography (PET/CT). The irreversible two-compartment model for FDG is used for description of this tracer, which enters first a free compartment C1, and afterwards it is metabolized irreversibly in the second compartment C2 (Hauser, 2013; Hauser et al, 2015). In order to determine the parameters of the model, information of the tracer delivery is needed in the form of the input function that represents the time-course of tracer concentration in the arterial blood or plasma. We use the Heaviside function to represent the IDAIF, because the transport of FDG across the arterial blood is very fast in the first few minutes and then it decreases slowly (Zhou, 2012). The Laplace transform method determines the analytical solution for the FDG two-tissue irreversible compartment

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model, with only approximation is the IDAIF.

Data used in this work was obtained from the Superagers project at the Instituto do Cérebro (InsCer/BraIns) at Pontifical Catholic University of Rio Grande do Sul (PUCRS) on a healthy 51-year-old, community-dwelling woman that underwent FDG PET/CT imaging.

The aim of this study is to compute the image-derived arterial input function by non-linear regression from the timeactivity curve in a carotid volume of interest(VOI), in FDG PET dynamic brain studies. The input function must be chosen in order to solve the exact form of the system of two differential equations to describe the dynamic behavior of the FDG tracer in brain dynamic PET studies.

2. The Proposed Method for Two-tissue Irreversible Compartment Model

The mathematical model for the FDG irreversible two compartment model, (Hauser et al, 2015), is expressed by the system of two differential equations

$$\begin{aligned} \frac{d}{dt}C_1(t) &= K_1\, C_a(t) - (\, k_2 + k_3\,)\, C_1(t) \\ \frac{d}{dt}C_2(t) &= k_3\; C_1(t) \\ C_1(0) &= 0\,, C_2(0) = 0\,, C_a(0) = 0, \end{aligned} \tag{1}$$

where $C_a(t)$ is IDAIF considered to be known, $C_1(t)$ and $C_2(t)$ are, respectively, the concentration within the nondisplaceable and displaceable compartments, $\frac{d}{dt}$ is the derivative operation with respect to time and K_1, and k_2, k_3 are positives proportionality rates, describing, respectively, the tracer influx into and the tracer outflow from the compartment(transport constants).

We apply the Laplace transform with respect to t in (1), denoting

$$\pounds\,\{\, C_i(t)\} = \overline{C}_i(s) = \int_0^\infty\; e^{-st}\, C_i(t)\, dt$$

and

$$\pounds\left\{\frac{d\, C_k(t)}{dt}\right\} = s\,\overline{C}_i(s) - C_i(0)\,.$$

We obtain, with $C_1(0) = 0$ and $C_2(0) = 0$, an algebric system:

$$\begin{aligned} (\, s + k_2 + k_3\,)\,\overline{C}_1(s) &= K_1\,\overline{C}_a(s) \\ -\, k_3\,\overline{C}_1(s) + s\;\overline{C}_2(s) &= 0\,. \end{aligned} \tag{2}$$

Now we apply the inverse Laplace transform to equation (2)

$$C_i(t) = \mathcal{L}^{-1}\left\{\overline{C}_i(s)\right\} .$$

Therefore, we obtain

$$\begin{aligned} C_1(t) &= \mathcal{L}^{-1}\left\{\frac{K_1\,\overline{C}_a(s)}{(\,s+k_2+k_3\,)}\right\} \\ C_2(t) &= \mathcal{L}^{-1}\left\{\frac{k_3\,\overline{C}_1(s)}{s}\right\} . \end{aligned} \tag{3}$$

Then,

$$\begin{aligned} C_1(t) &= K_1\,\mathcal{L}^{-1}\left\{\frac{1}{(\,s+k_2+k_3\,)}\right\} * \mathcal{L}^{-1}\left\{\overline{C}_a(s)\right\} \\ C_2(t) &= k_3 * \mathcal{L}^{-1}\left\{\overline{C}_1(s)\right\} , \end{aligned} \tag{4}$$

where $*$ denotes the convolution operation.

The representation (4) implies that

$$\begin{aligned} C_1(t) &= K_1\,e^{-(\,k_2+k_3\,)\,t} * C_a(t) = K_1\int_0^t e^{-(\,k_2+k_3\,)\,(t-u)}\;C_a(u)\,du \\ C_2(t) &= k_3 * C_1(t) = k_3\int_0^t C_1(u)\,du\;. \end{aligned} \tag{5}$$

Then, with $\lambda = k_2 + k_3 > 0$, the analytical solution of the irreversible two compartment model for FDG (1) is

$$\begin{aligned} C_1(t) &= K_1\,e^{-\lambda\,t}\int_0^t e^{\lambda\,u}\;C_a(u)\,du \\ C_2(t) &= k_3\int_0^t C_1(u)\,du\;. \end{aligned} \tag{6}$$

It is important now to choose a suitable model to represent the the input function $C_a(t)$, which makes it possible to calculate the integral

$$I = \int_0^t e^{\lambda\,u}\;K_1\,C_a(u)\,du\,. \tag{7}$$

3. Carotids Image-Derived Arterial Input Function (IDAIF)

The dynamics of the radiotracer in a reference region is governed by the differential equation (Su et al, 2013)

$$\begin{aligned} \frac{dC_r}{dt} &= K_1^{'}C_a(t) - k_2^{'}C_r(t) \\ C_r(0) &= 0 \end{aligned} \tag{8}$$

where $C_a(t)$ is the concentration of the radiotracer in the arterial blood, $C_r(t)$ is the concentration of the radiotracer in the reference region and $K_1{}' > 0$ and $k_2{}' > 0$ are proportionality rates, describing, respectively, the tracer influx into and the tracer outflow from the reference tissue.

Then, $C_a(t)$, the IDAIF, is given by

$$C_a(t) = \frac{1}{K_1^{'}}\frac{dC_r}{dt} + \frac{k_2^{'}}{K_1^{'}}C_r(t) \tag{9}$$

The effective dose injected can be calculated as:

$$C_a(0) = C_a^i e^{-\frac{ln2}{t_{1/2}}(t_0 - t_i)} - C_a^e e^{-\frac{ln2}{t_{1/2}}(t_e - t_0)} \tag{10}$$

where C_a^i is the dose measured before injection at time t_i, C_a^e is the residual dose after injection measured at time t_e, and $t_{1/2}$ is the half-time of the tracer.

We need to consider that the transport of FDG across de arterial blood is very fast in the first few minutes and then decreases slowly (Zaidi H, 2006; Zhou, 2012). We estimate the arterial input function in three stages and solve nonlinear regressions. First, we approximate $C_r(t)$ by means of nonlinear regression of the data obtained from a TAC curve on a Positron Emission Tomography(PET) image, as piecewise function

$$C_r(t) = (H(t-t_0) - H(t-t_1))C_{rf}(t) + (H(t-t_1) - H(t-t_2))C_{rI}(t) + H(t-t_2)C_{rs}(t),$$

where $C_{rf}(t)$, $C_{rI}(t)$ and $C_{rs}(t)$ are the concentration of the radiotracer on the reference region, respectively, for the fast, intermediate and slow stage. $H(t)$ is the Heaviside function defined by

$$H(t-a) = \begin{cases} 0, t < a, \\ 1, t \geq a. \end{cases} \tag{11}$$

$$H(t-a) - H(t-b) = \begin{cases} 0, t < a \ and \ t \geq b, \\ 1, a \leq t < b. \end{cases} \tag{12}$$

4. Numerical Results and Final Considerations

A healthy 51-year-old, community-dwelling woman included in the Super Agers project underwent cognitive testing, neuroimaging assessment and PET/CT imaging with Fluorodeoxiglucose (FDG). She had no family history of dementia or any medical conditions were reported. She signed the informed consent previously approved by the local medical ethics committee. The clinical and neuropsychological evaluation confirmed the absence of previous story of neurological or psychiatric disease or use of any type of medication, and cognitive scores normal for age. Specifically, she performed 28 in the Mini-Mental State Examination (out of 30), 13 in the Rey Auditory-Verbal Learning Test (out of 15), 38 in the Phonemic Fluency (0.75 Standard Deviation of the mean for age and education) and 89 in the Trail-Making Test B (-0.47 standard deviation of the mean for age and education), based on previous studies (Reitan, 1979; Harrison et al, 2012).

Dynamic [18F] FDG-PET images were collected at the Brain Institute of Rio Grande do Sul. Imaging was acquired in a PET GE Discovery 600 scanner. First, a regular CT scan was obtained for attenuation and scatter correction of the subsequent emission sequence. Then, PET data was acquired in list mode. Before performing the PET scan, the patient was immobilized to minimize motion during the scan. Data was collected in DICOM format and then processed using the biomedical image quantification software PMOD (PMOD Technologies LLC, Zurich, Switzerland). The use of PMOD has been described by many studies in extracting VOI values, (Kuhn et al, 2014; Pagani et al, 2017; Shaikh et al, 2015). The calibrated dose in Syringe was 284160kBq and the remainning dose was 39035kBq. We consider the half-life for 18F-FDG of 109.77 minutes (Hays et al, 2002).

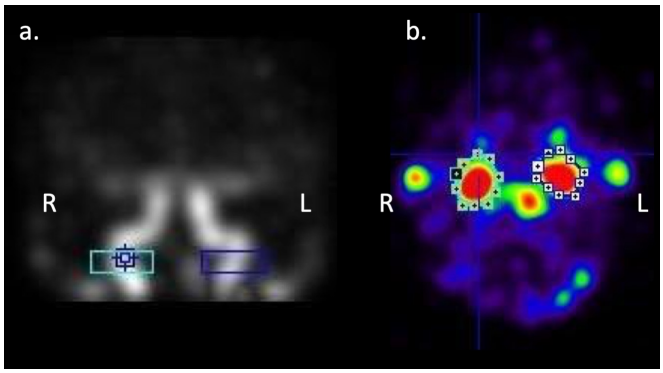

Figure 1. Bilateral carotid Volume-of-Interest (VOI) using (a) MIP (Maximum Intensity Projection) image and (b) PET image.

We manually define Volumes-of-Interest (VOIs), illustrated in Figure 1, using PMOD. Left and right carotid arteries were identified on the fifth frame. According to the PMOD users manual, VOIs are built from planar polygons called contours (CTR), with axial orientation. Use the mouse wheel, or the slices slider, to scroll to the axial three slices , and outline the right carotid there similarly. The R carotid VOI now consists of 3 ROIs, each containing 1 CTR. For those VOIs,over which the left and right

carotid arteries where clearly visible, is defined discrete time activity curves(TACs) and is generated the average TAC. Afther this we apply regression techniques, (Marquardt, 1963), and we obtain:

- whit correlation coefficient 0.99, the linear as the best model for $C_{rf}(t)$:

$$C_{rf}(t) = 1022.51 * t\,;$$

- whit correlation coefficient 0.98 ,the saturation growth-rate model as the best model for $C_{rI}(t)$:

$$C_{rI}(t) = \frac{7612.38\,t}{-25.10 + t}\,;$$

- whit correlation coefficient 0.95, the saturation growth-rate model as the best model for $C_{rs}(t)$:

$$C_{rs}(t) = \frac{8113.45\,t}{-24.84 + t}\,.$$

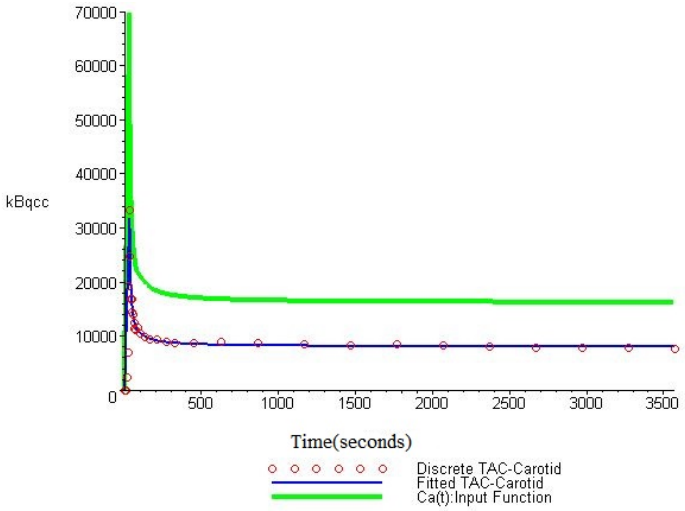

Figure 2. Discrete and Fitted Carotid Time Active Curve and The Input Function.

We approximate $C_r(t)$ by means of nonlinear regression of the data obtained from a TAC curve on a Positron Emission Tomography(PET) image, as piecewise function

$$C_r(t) = (H(t-.0005) - H(t-32.5))C_{rf}(t) + (H(t-32.5) - H(t-85))C_{rI}(t) + H(t-85)C_{rs}(t),$$

where $C_{rf}(t)$, $C_{rI}(t)$ and $C_{rs}(t)$ are the concentration of the radiotracer on the reference region, respectively, for the fast, intermediate and slow stages and $H(t)$ is the Heaviside function defined in Eq.(11). Then, we obtain the IDAIF $C_a(t)$ using the system for symbolic mathematical computation MAPLE to solve Eq.(9).

The Carotid fitted, TAC $C_r(t)$ and the IDAIF $C_a(t)$ are shown in Figure 2 and the main purpose of the study was achieved.

In summary, we describe a non-invasive method of estimation of the input function in the FDG positron emission tomography dynamic brain. The main contribution is that we used the Heaviside function to represent the image derived carotid arterial input function as piecewise function which allows to calculate the exact solution of the two-tissue reversible compartment model. Cumulative errors occurred only in determining the arterial input function, where the lowest correlation coefficient was 0.95 in the $C_rs(t)$. This study provides evidence towards a solution to the complex puzzle of a non-invasive method for dynamic brain PET evaluation. Ultimately, a non-invasive method will be more adequate for image quantification in the clinical setting.

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