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APATHY IN ACUTE STROKE AND APATHETIC PERSONALITY DISTURBANCE SECONDARY TO STROKE

Lara Isabel Pires de Melo Caeiro

Doutoramento em Ciências e Tecnologias da Saúde

Especialidade em Desenvolvimento Social e Humano

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De coração,

Dedico este trabalho ao David, meu marido Querido

E à minha Querida filha, a Sofia

“ONE morning… there was lying in bed a gentleman named Ilya Ilyitch Oblomov. He was a fellow of a little over thirty, of medium height, and of pleasant exterior. Unfortunately, in his dark-grey eyes there was an absence of any definite idea ... Suddenly a thought would wander across his face… Then it would disappear, and once more his face would glow with a radiant insouciance which extended even to his attitude and the folds of his night-robe...

Even when excited, his actions were governed by an unvarying gentleness, added to a lassitude that was not devoid of a certain peculiar grace…

In Oblomov's eyes it was a garment possessed of a myriad invaluable qualities, for it was so soft and pliable that, when wearing it, the body was unaware of its presence, and, like an obedient slave, it answered even to the slightest movement… With Oblomov, lying in bed was neither a necessity (as in the case of an invalid or of a man who stands badly in need of sleep) nor an accident (as in the case of a man who is feeling worn out) nor a gratification (as in the case of a man who is purely lazy)… almost always he was at home--he would spend his time in lying on his back.

True, on the whatnots there were two or three open books, while a newspaper was tossing about, and the bureau bore on its top an inkstand and a few pens; but the pages at which the books were lying open were covered with dust and beginning to turn yellow (thus proving that they had long been tossed aside), the date of the newspaper belonged to the previous year...”

In “Oblomov”

By Ivan Goncharov [1858]

ÍNDICE

A ESCOLHA DO TEMA DA TESE

Os cuidados de Saúde Mental e a prevenção da doença mental secundária a doenças específicas são áreas importantes de investigação e de aplicação psicológica e médica. A doença mental secundária ao Acidente Vascular Cerebral (AVC) é bastante reconhecida e tem sido alvo de tratamento tanto na fase aguda do AVC como após o AVC, baseado no facto de a doença mental secundária ao AVC ser um facto incapacitante para que o doente possa voltar à sua vida familiar, social e laboral.

Escolhemos investigar a doença mental secundária ao AVC porque o AVC é a principal causa de morte e uma das grandes causas de incapacidade física, psiquiátrica e psicológica em Portugal, tendo enorme impacto pessoal e económico para o doente, para a família ou cuidador, e no sistema de cuidados de saúde.

As doenças mentais e os consequentes distúrbios comportamentais secundários ao AVC representam uma alteração na vida do doente e do seu núcleo familiar por três razões: 1) por haver necessidade de facultar cuidados de saúde ao doente, 2) pelo facto de haver diminuição do sentido de pertença social e de produtividade do doente e do cuidador do doente, pois ambos reduzem a sua atividade social e profissional, momentânea ou permanentemente, e também 3) pelo aumento da possibilidade do mesmo cuidador vir a desenvolver uma doença mental, enquanto prestador de cuidados ao doente. Assim sendo, identificar e reduzir a doença mental secundária a um AVC pode ser importante tanto para o doente como para o cuidador.

Ainda não foram completamente estudadas as repercussões a logo prazo da doença mental secundária ao AVC, e em particular da alteração da personalidade tipo apático secundária ao AVC. A alteração da personalidade tipo apático secundaria ao AVC é um distúrbio com alterações do comportamento do paciente, e que este ou os seus cuidadores caracterizam como “parado” ou “indiferente”. Apesar de comuns e frequentes, os distúrbios comportamentais são muitas vezes negligenciados, enquanto complicação médica [APA, 2002], levando a que a sua deteção, tratamento e reabilitação sejam dificultadas ou mesmo ineficazes porque tardias.

PUBLICAÇÕES RESULTANTES DA TESE

Da presente dissertação resultaram 3 artigos científicos já publicados em 2013.

O primeiro artigo, *Apathy Secondary to Stroke: A Systematic Review and Meta-Analysis*, foi publicado em Janeiro de 2013 na revista *Cerebrovascular Diseases*. O mesmo pode ser consultado no capítulo 3 desta dissertação. (Caeiro L, Ferro JM, Costa J (2013). Apathy Secondary to Stroke: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases 35:23-39)

O segundo artigo, *Metric Properties of the Portuguese Version of the Apathy Evaluation Scale*, foi publicado em Dezembro de 2012, na revista *Psicologia, Saúde & Doenças*. O mesmo pode ser consultado no capítulo 4 desta dissertação. (Caeiro L, Silva T, Ferro JM, Pais-Ribeiro J, Figueira ML (2012). Metric properties of the Portuguese version of the Apathy Evaluation Scale. Psicologia, Saúde & Doenças 13:266-282)

O terceiro artigo, *Post-Stroke Apathy: An Exploratory Longitudinal Study*, foi publicado em Junho de 2013 na revista *Cerebrovascular Diseases*. O mesmo pode ser consultado no capítulo 5 desta dissertação. (Caeiro L, Ferro JM, Melo TP, Canhão P, Figueira ML (2013). Post-Stroke Apathy: An Exploratory Longitudinal Study. Cerebrovascular Diseases;35:507–513)

Cada um dos capítulos (3 a 5) inclui o texto e figuras que correspondem exatamente aos artigos originais.Desta forma, optámos por não incluir uma cópia dos artigos originais publicados nas revistas científicas. No entanto, apenas para melhorar a aparência editorial da presente dissertação, cada capítulo apresenta uma edição diferente da apresentada nos artigos originais.

PALAVRAS CHAVE

Apathy; Motivation; Depression; Verbal Abstract Reasoning; Stroke

ABREVIAÇÕES

ACC	Anterior Cingulate Cortex
AES-C	Apathy Evaluation Scale, Clinical-rated
AES-S	Apathy Evaluation Scale, Self-rated
AI	Anterior Insula
ATL	Anterior Temporal Lobe
BF	Basal Forebrain
BLAD	Bateria de Lisboa de Avaliação da Demência
CT	Computed Tomography
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Revision, 4th Edtion
EuroQol	Questionnaire of Quality of Life
EQ-VAS/Health	self-rated heath status
ICD-10	International Classification of Diseases, 10th version
GCS	Glasgow Coma Scale
MADRS	Montgomery Åsberg Depression Rating Scale
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NA	Nucleus Accumbens
NIHSS	Neurological Institute Health Stroke Scale
OFC	Orbitofrontal Cortex
PAG	Periacqueductal Gray Matter
PCC	Posterior Cingulate Córtex
PNS	National Healthcare Plan
SAH	Subarachnoid Hemorrhage
VMPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area

ABSTRACT

In this thesis we investigated apathy secondary to stroke, both in acute and in post-acute phases.

We aimed at studying apathy at 1-year after stroke and its relationship with apathy in acute stroke, demographic, pre-stroke predisposing conditions and clinical features (stroke type and location), post-stroke depression and cognitive impairment, functional outcome, and Quality of Life and Health.

Apathy is a disturbance of motivation evidenced by low initiative, difficulties in starting, sustaining or finishing any goal-directed activity, low self-activation or self-initiated behaviour and/or emotional indifference. Caregivers often describe patients as presenting loss of initiative, emotional indifference and unconcern, which only became apparent after stroke. This disturbance is defined by the DSM-IV-TR clinical criteria as Personality Change Due to Stroke-Apathetic Type.

Apathy may be mistaken as depression or as a detachment on caregivers to whom patients were emotionally attached previously. This state is not seen by the patient as a reason to complain to relatives or doctors, and patients accepted this new way of living and often do not report as problematic.

To start our research on post-stroke apathy we performed a systematic review to better estimate its rate and relationship with associated factors, as well as to explore if apathy is associated with a poorer clinical outcome (Chapter 3: *Apathy secondary to stroke: a systematic review and meta-analysis*). A total of 19 different stroke samples were included for analysis. The frequency of apathetic patients ranged between 15.2 to 71.1%. Pooled rate of apathy secondary to stroke was 36.3% (95%CI 30.3 to 42.8%). In the acute phase the rate of apathy was 39.5%, and in the post-acute phase the rate was 34.3%. Apathy rate was significantly higher in any-stroke (first-ever or recurrence of stroke) studies (41.6%; I2=44.9%) compared with studies including only first-ever strokes. Apathetic patients are about 3 years older than non-apathetic patients. Apathy was a common condition in older persons and in particular in older cognitively impaired people and stroke is a risk factor for apathy in both. The rate of “pure” apathy (without concomitant depression) was twice as frequent as the rate of “pure” depression (without concomitant apathy). These two neuropsychiatric disturbances were not associated, in spite of the concomitance of both in one third of the samples of stroke patients. Apathetic patients were more frequently and severely depressed in comparison to non-apathetic patients. The rate of apathy secondary to stroke was similar for left and right-sided hemispheric stroke lesions and for ischemic and hemorrhagic stroke type. Finally, apathy secondary to stroke had a negative impact on

clinical global outcome only if apathetic patients were first-ever stroke and were younger. The apparent discrepancy of our finding may be related to characteristics of apathy itself because apathetic patients may be less aware or report fewer complains about a loss of functionality. It also can be due to the fact that not all the original studies present a relationship between apathy and the factors.

We performed a preliminary study aiming at describing the metric properties of the clinical-rated (AES-C) and self-rated (AES-S) versions of the Apathy Evaluation Scale (Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*). This study was the baseline for the achievement of the other five goals proposed (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*), which depended on this one. The AES-C and the AES-S are validated for English language. The Apathy Evaluation Scale is useful to characterize and quantify apathy. We included 156 “healthy participants”, 40 healthy “elderly participants”, 21 patients with dementia, and 21 patients with depression, comprising a sample of 238 individuals. The AES-C (Cronbach α=.82; Split-half=.67) and the AES-S (Cronbach α=.81; Split-half=.60) showed good construct validity and high internal consistency. The items that loaded onto the analysis of principal components for the AES-C and AES-S were quite similar. The cut-off point of AES-C was dependent on the educational level (0-4 years of education= 38; 5-9 years=37; ≥10 years=30). The cut-off point of the AES-S was 39 points. The comparison among the four samples revealed that patients with dementia had higher scores in the AES-C. For the AES-S healthy participants scored themselves with the lowest mean scores. The Portuguese versions of the AES-C and of the AES-S were reliable and valid instruments to measure apathy in Portuguese speaking individuals.

The first goal of our principal study aimed at describing the frequencies of post-stroke apathy at 1-year after stroke. Additionally, we aimed at finding out, which was the relationship between apathy in acute stroke and post-stroke apathy. (Chapter 5: *Post-Stroke Apathy: An Exploratory Longitudinal Study*). In the study on post-stroke clinical-rated apathy we identified 22.4% in acute stroke phase and 23.7% of post-stroke apathy at 1-year follow-up. In our multivariate model apathy in acute stroke (OR=3.8) was an independent factor for post-stroke apathy at 1-year follow-up. Apathy in acute stroke was a predictor of 41% of post-stroke apathy; two-fifths of the patients with acute apathy may still be apathetic at 1-year follow-up. We found that apathy in acute stroke increased the risk of post-stroke apathy in almost four-time fold. Nevertheless, 61% of the post-stroke apathy cases were identified at follow-up, which highlights for the importance of the evaluation of apathy at follow-up.

The second goal aimed at analysing the relationship between post-stroke apathy and a specific acute stroke location (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*). No associations were found between post-stroke apathy and stroke location, but we found a trend of an association with hemispheric stroke location. Lesions in the cerebellum or at the brainstem are not involved in motivation disturbances and were not related to post-stroke apathy. In our systematic review there was no sufficient data to support conclusions, however one fact became apparent that older patients presenting left-sided stroke lesions had a significant higher rate of apathy (either acute or post-acute).

The third goal of our principal study had the purpose to analyse the relationship between post-stroke apathy and post-stroke cognitive impairment (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*). We found that, at 1-year follow-up, post-stroke verbal abstract reasoning impairment was an independent risk factor for post-stroke apathy, increasing the risk of post-stroke apathy by seven-time fold. Apathetic patient's thinking relies on a non-abstract process but instead on a concrete dimension. Abstract reasoning ability is an important prerequisite for the use of prior learning in new contexts or to the way in which prior learning affects new learning and performance. The improvement of abstract reasoning is important for patients who, due to brain lesion, have difficulties in their daily living activities.

The fourth goal of our study aimed at making the analysis of the relationship between post-stroke apathy and post-stroke depression (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*). In our sample post-stroke apathy and depression were present in a quarter of our patients, but in three quarters the two clinical neuropsychiatric disturbances were independent one from the other. In our systematic review (Chapter 3: *Apathy secondary to stroke: a systematic review and meta-analysis*) apathetic patients were more severely depressed mostly in the acute phase of stroke and for younger patients.

The fifth goal aimed at analysing the relationship between post-stroke apathy and late outcome (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*). We found a relationship between post-stroke apathy and bad functional outcome. Nevertheless, apathetic post-stroke patients did not report a loss in quality of life or in self-perception of health, when compared with non-apathetic post-stroke patients. In our systematic review (Chapter 3: *Apathy secondary to stroke: a systematic review and meta-analysis*) we did not confirm that apathetic patients had worse clinical global outcome, however there is a trend for patients with first-ever stroke and younger patients present poorer clinical global outcome.

RESUMO

Nesta tese investigámos a apatia secundária ao Acidente Vascular Cerebral (AVC), tanto durante a fase aguda como na fase pós-aguda do AVC (após AVC).

Tivemos como objetivo o estudo da apatia ao 1º ano após o AVC e a relação desta com a presença de apatia na fase aguda do AVC, fatores demográficos, condições predisponentes prévias ao AVC e variáveis clínicas (tipo e localização do AVC), depressão e defeito cognitivo após AVC, estado funcional e Qualidade de Vida e perceção de saúde.

A apatia é um distúrbio da motivação que se evidencia por baixa da capacidade de iniciativa, por dificuldades em iniciar, suster e finalizar uma atividade dirigida a um objetivo, por uma auto-ativação ou comportamento auto-iniciado baixo e/ou indiferença emocional. Os cuidadores frequentemente descrevem os seus pacientes como apresentando perda da iniciativa, indiferença emocional e despreocupação, apenas observáveis após o AVC. Esta perturbação pode ser clinicamente definida no DSM-IV-TR como uma Perturbação da Personalidade secundária ao AVC – Tipo Apático.

A apatia pode ser confundida com depressão ou desapego aos cuidadores, aos quais o paciente esteve emocionalmente ligado. Este estado não é visto ou sentido pelo paciente como um estado que requeira preocupação e consequentemente como algo de que se queixar ao seu médico ou aos seus familiares. Os pacientes frequentemente aceitam esta nova forma de estar ou de viver e não a reportam como algo problemático.

Para iniciar a nossa investigação sobre a apatia após o AVC fizemos uma revisão sistemática e recorremos à meta-análise. Pretendemos estimar a frequência da apatia secundária ao AVC e a relação desta com fatores associados, bem como explorar se a apatia estaria associada a um mau prognóstico clínico (Capítulo 3: *Apathy secondary to stroke: a systematic review and meta-analysis*). No total foram incluídas na análise sistemática 19 amostras de pacientes com AVC. A frequência de pacientes apáticos variou entre 15.2 e 71.1%. O global das frequências de apatia secundária ao AVC foi de 36.3% (IC 95% 30.3 a 42.8%). Especificamente na fase aguda do AVC a frequência de apatia foi de 39.5% e na fase após AVC a frequência foi de 34.3%. A frequência de apatia foi significativamente maior nos estudos que incluíam qualquer tipo de pacientes (incluindo 1º AVC e recorrência de AVC) (41.6%; I2=44.9%) comparativamente aos estudos incluindo apenas pacientes com 1º AVC. Os pacientes apáticos eram cerca de 3 anos mais velhos que os pacientes não apáticos. A apatia era uma condição comum em pacientes mais velhos e, em particular, em pacientes mais velhos com defeito cognitivo. O AVC é um fator de risco para o surgimento de apatia em qualquer destes. A frequência de apatia “pura” (sem depressão concomitante) foi o dobro da frequência de depressão “pura” (sem apatia

concomitante). Estes dois distúrbios neuropsicológicos não estavam associados, apesar de cerca de um terço das amostras de pacientes com AVC apresentar ambos. Os pacientes apáticos eram mais frequente e severamente depressivos comparativamente aos pacientes não apáticos. A frequência de apatia secundária ao AVC foi similar em doentes com AVC do hemisfério direito e esquerdo, bem como para pacientes com AVC isquémico ou hemorrágico. Finalmente, a apatia secundária ao AVC teve um impacto negativo no estado clínico global final apenas em pacientes com 1º AVC e em pacientes mais jovens. A aparente discrepância entre os nossos dados obtidos através da meta-análise e os estudos originais pode estar relacionada com as características da própria apatia, porque os doentes apáticos podem reconhecer menos frequentemente e queixarem-se menos da perda da sua funcionalidade. Também pode dever-se ao facto de nem todos os estudos constatarem uma relação entre a apatia e os fatores estudados.

Realizámos também um estudo preliminar que teve como objetivo descrever as propriedades métricas das versões clinica (AES-C) e de auto-avaliação (AES-S) da Escala de Avaliação da Apatia (Capítulo 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*). Este objetivo foi o ponto de partida para atingirmos os outros cinco objetivos a que nos propusemos no estudo principal (Capítulo 5: *Post-Stroke apathy: An Exploratory longitudinal study*), os quais estavam dependentes deste. A AES-C e a AES-S estão validadas na versão original inglesa. A AES é utilizada para caracterizar e quantificar a apatia. Estudámos uma amostra de 156 "participantes saudáveis", 40 "participantes idosos saudáveis" de um centro de dia, 21 pacientes com demência e 21 pacientes com depressão, perfazendo uma amostra total de 238 indivíduos. Estudámos o nível de fidelidade através do Alpha (α) de Cronbach e do método *Split-half,* bem como a validade de constructo através da análise dos componentes principais com rotação de Varimax. Na sua versão Portuguesa, tanto a AES-C (Cronbach α=.82; Split-half=.67) como a AES-S (Cronbach α=.81; Split-half=.60) apresentaram boa validade de constructo e uma boa consistência interna. Os itens incluídos na análise de principais componentes da AES-C e AES-S eram similares. O ponto de corte da AES-C esteve dependente do nível de educação (0-4 anos de educação= 38 pontos; 5-9 anos=37 pontos; ≥10 anos=30 pontos) e o ponto de corte da AES-S foi de 39 pontos. A comparação entre as quatro amostras revelou que os pacientes com demência apresentaram pontuações mais altas na AES-C. Relativamente à AES-S, os participantes saudáveis apresentaram as pontuações mais baixas. As versões portuguesas da AES-C e da AES-S mostraram ser instrumentos válidos para medir a apatia em sujeitos portugueses.

O nosso estudo principal teve como primeiro objetivo descrever as frequências da apatia 1 ano após AVC. Adicionalmente, tivemos como objetivo descobrir qual a relação

entre a apatia na fase aguda e a apatia após AVC (Capitulo 5: *Post-Stroke Apathy: An Exploratory Longitudinal Study*). Neste estudo, a apatia avaliada clinicamente foi identificada em 22.4% dos pacientes na fase aguda e em 23.7% na fase após AVC. No modelo estatístico multivariado, a apatia na fase aguda (OR=3.8) foi um fator independente para a apatia após AVC. A apatia na fase aguda foi um preditor de 41% dos casos de apatia após AVC; ou seja, dois quintos dos pacientes com apatia na fase aguda permaneceram apáticos ao 1 ano após AVC. Descobrimos que a apatia na fase aguda do AVC quase quadruplicava o risco de apatia após AVC. Não obstante, 61% dos casos com apatia após AVC foram apenas identificados durante o seguimento, o que denota a importância da avaliação da apatia nas consultas de seguimento.

O segundo objetivo teve como propósito analisar a relação entre a apatia após AVC e uma lesão aguda específica originada pelo AVC (Capítulo 5: *Post-Stroke apathy: An Exploratory longitudinal study*). Não se encontraram associações entre a apatia após AVC e a localização da lesão em fase aguda do AVC. No entanto, encontrou-se uma tendência associativa relativamente à localização hemisférica da lesão. As lesões do cerebelo e do tronco não estavam envolvidas nos distúrbios da motivação nem estavam relacionadas com a apatia após AVC. Na revisão sistemática que realizámos não houve dados suficientes que permitissem suportar qualquer conclusão; contudo, realçou o facto de os pacientes mais velhos e com lesões lateralizadas à esquerda apresentarem frequências de apatia mais elevadas (tanto na fase aguda como após AVC).

O terceiro objetivo do nosso estudo principal pretendia analisar a relação entre a apatia após AVC e o defeito cognitivo após AVC (Capítulo 5: *Post-Stroke apathy: An Exploratory longitudinal study*). Após 1 ano de seguimento, o défice do raciocínio abstrato verbal foi identificado como sendo um fator de risco independente para a apatia após AVC, incrementando o risco de apatia após AVC em sete vezes. O raciocínio dos pacientes apáticos baseia-se não num pensamento abstrato mas sim num pensamento concreto. A capacidade de raciocínio abstrato é um pré-requisito importante para que o sujeito utilize a aprendizagem prévia em novos contextos ou para que essa aprendizagem afete as novas aprendizagens e as novas realizações. A possibilidade de recuperar o raciocínio abstrato é importante para os pacientes que, devido a uma lesão cerebral, têm dificuldades nas atividades de vida diária.

O quarto objetivo do nosso estudo principal tinha como propósito analisar a relação entre a apatia após AVC e a depressão após AVC (Capítulo 5: *Post-Stroke apathy: An Exploratory longitudinal study*). Na nossa amostra, a apatia após AVC e a depressão estavam presentes em um quarto dos pacientes com AVC. No entanto, em três quartos do

grupo de pacientes os dois distúrbios neuropsiquiátricos eram independentes um do outro. Na nossa revisão sistemática (Capítulo 3: *Apathy secondary to stroke: a systematic review and meta-analysis*) os pacientes apáticos estavam mais severamente deprimidos, particularmente na fase aguda do AVC e os pacientes mais novos.

O quinto objetivo do nosso estudo pretendeu analisar a relação entre a apatia após AVC e a funcionalidade clínica (Capítulo 5: *Post-Stroke apathy: An Exploratory longitudinal study*). No nosso estudo encontrámos uma relação entra a apatia após AVC e uma má funcionalidade. Contudo, os pacientes apresentando apatia após AVC não revelaram ter perdido nem Qualidade de Vida nem saúde em comparação com pacientes sem apatia. Na nossa revisão sistemática (Capítulo 3: *Apathy secondary to stroke: a systematic review and meta-analysis*) não confirmámos que os pacientes apáticos apresentassem pior funcionalidade clínica. No entanto, identificámos uma tendência de associação entre a perda de funcionalidade clínica e o facto de serem pacientes com primeiro AVC ou pacientes mais novos.

THE STUDY OF APATHY
IN STROKE PATIENTS

STATE OF THE ART
A NARRATIVE REVIEW

“Um estudo dos nervos fica incompleto se o anatomista não souber, por via própria, o que é a dor ou o prazer.”

Ribot, 1870

[in *La psychologie anglaise contemporaine (École expérimentale).* Paris: Libraire Philosophique de Ladrange]

ABSTRACT

Apathy is a disorder of motivation that can be followed for abulia, avolition, athymormia or emotional indifference. The DSM-IV-TR clinical criteria Personality Change Due to Stroke-Apathetic Type (Post-stroke Apathy) is the only one suitable for the purposes of this study. Apathetic patients have difficulties in starting, sustaining or finishing any goal-direct activity. They have low interest in doing things and loose self-activation or self-initiated behaviour.

There are several scales or inventories used to assess apathy. In the assessment of apathy, it is of most importance to observe not only motivation but also behaviour, thinking, and emotional response.

Motivational disturbances such as apathy have been related to damage to subcortical brain structures linked to the anterior cingulate circuit, the so-called motivational circuit.

In the few studies with stroke patients, the incidence of apathy in stroke patients range between 15.2% to 91.7%. Some studies claimed an association between apathy and stroke location and right-sided stroke lesion, however there is no consistent evidence to support this association. Stroke lesions associated with apathy encompass the frontal lobe, the cingulate gyrus or subcortical structures such as the globus pallidus, internal capsule, caudate, putamen, and anterior or medial thalamic nuclei. Evidence from studies on apathy after stroke reported contradictory findings concerning associated conditions such as depression, cognitive impairment, and outcome.

Although apathy and depression after stroke can be associated, each one of these neuropsychiatric disturbances can occur separately from the other. Impaired cognition is an associated condition but findings are contradictory. Probably the executive type cognitive domain is the one that is mostly related to post-stroke apathy. Several studies report associations between apathy and low functional status but among other studies there no association was found.

Further longitudinal studies are needed to understand the relationship between apathy in the acute and in post-acute phases of stroke. Clarification of the association between post-stroke apathy and stroke type and location, and between depression and executive-like cognitive impairments is necessary. There is still missing information on the consequences of post-stroke apathy and functional outcome of these stroke patients.

RESUMO

A apatia é uma perturbação da motivação que pode ser acompanhada por abulia, avolição, atimormia ou indiferença emocional. O critério clínico descrito no DSM-IV-TR de Perturbação da Personalidade Secundária a um AVC – Tipo Apático (Apatia Após o AVC) é o único que se adequa aos propósitos deste estudo. Os pacientes apáticos têm dificuldades em iniciar, conitnuar e acabar uma actividade dirigida ao objectivo. Estes pacientes têm baixo interesse em realizar actividades e perdem a capacidade de auto-activação e de terem comportamentos por iniciativa própria.

Existem diversas escalas ou inventários usados para avaliar a apatia. Na avaliação da apatia é muito importante observar não só a motivação do paciente, mas também o comportamento, o pensamento e a resposta emocional.

A apatia está relacionada com lesões cerebrais envolvendo estruturas subcorticais directamente ligadas ao circuito cingulado, também designado por circuito da motivação.

Nos poucos estudos feitos em pacientes com AVC, a incidência de apatia secundária ao AVC, varia entre 15.2% a 91.7%. Alguns estudos demonstram uma associação entre a apatia e a localização do AVC e lesão cerebral no hemisfério direito. No entanto, não a evidência não é consistente para suportar esta associação. As lesões por AVC associadas à apatia envolvem o lobo frontal, circunvolução do cingulo ou estruturas subcorticais como o globo pálido, cápsula interna, núcleo caudado, putamen e núcleos anterior a medial do tálamo.

A evidência resultante dos estudos sobre a apatia após o AVC apresenta resultados contraditórios relativamente à associação com variáveis como a depressão, défice cognitivo e estado funcional. Apesar da apatia e da depressão após o AVC poderem estar associados, cada uma destas perturbações neuropsiquiátricas pode surgir separadamente uma da outra. O défice cognitivo é uma condição associada mas os dados também são contraditórios. Provavelmente, o domínio cognitivo das funções executivas é aquele que está mais relacionado com a apatia após o AVC. Vários estudos apresentam associações entre a apatia e o défice functional, mas noutros esta associação não foi encontrada.

Mais estudos longitudinais são necessarios para a compreensão da relação entre a apatia na fase aguda e pós-aguda do AVC. É necessária a clarificação da associção entre a apatia e o tipo e localização do AVC, depressão e défices cognitivos executivos. Faltam ainda informações mais consistentes sobre as consequências da apatia após o AVC e o défice funcional destes pacientes.

1. INTRODUCTION

The most recent issue of the Portuguese “Plano Nacional de Saúde” (National Healthcare Plan - PNS), based on the Healthcare National System [1], defined that illness, its implications in quality of life, functional impairment, long term health care and expenses, and scientific research should be goal-directive issues for the following years. In the same PNS, clinical research has been offering several approaches to understand health and disease. Investigation has been providing an important understanding of the patients and caregivers needs in health, disease, acute care, long-term care and social and economic support.

A strategic goal of PNS contemplated the improvement of cerebrovascular diseases/stroke management in adults and in particular in elderly adults.

We chose to investigate mental diseases secondary to stroke because stroke is the leading cause of death and disability in Portugal, with enormous economic impact on the individual, the family/caregiver and on the healthcare system. Portugal is the country with the highest rate of post-stroke mortality in Western Europe. In 1990 the risk of death due to stroke was of 129/100.000 for men and 107/100.000 for women [2]. In 2010, the risk of post-stroke mortality was of 80/100.000 [3]. Younger populations have a risk of mortality of 7.3 to 54.9/100.000 inhabitants and elderly populations have a risk of mortality of 1102.3/100.000 inhabitants [1] [Page 30, Table 5], turning this disease a priority for the Portuguese healthcare system.

In general, mental diseases represent an huge expense based on the healthcare provision to the patient, and based on the absence of productivity of the youngest patients or of the caregiver in their own activity and the great probability of the latter becoming a patient himself due to exhaustion [4].

Mental care and prevention of mental disease secondary to a specific disease has become an important area of research, medical concerning and clinical practice. Mental disease secondary to stroke, has been increasingly recognized and has become a goal in medical treatment. Mental disease secondary to stroke frequently unables patients to return to their familiar/social/working life, and increases the risk of death and of developing other chronic mental or physical illness [5]. In the elderly, patients are in greater risk of stroke, of mental disease and of affective and social isolation. Age, stroke and isolation are risk factors for mental disease [4].

Behavioural disturbances are one of the possible complications of stroke [6]. Stroke itself may result in physical handicaps, which may frustrate the patient, or create uncertainties about the future, and enforced dependency and imposition of an invalid role. Later on, the patient may face loss of job or status, financial insecurity, a sense of uselessness or the prospect of permanent loss of independence. For stroke patients, handicaps and dependency may cause catastrophic reaction, depression or anxiety disorders, but for other stroke patients, it may not trigger any type of reaction or emotion at all, and these patients show Personality Change Due to Stroke-Apathetic Type. About half of the pre-working stroke patients do not return to work in post stroke period due to psychological or cognitive morbidity or physical disability [7].

There are few systematic investigations on the prevalence of behavioural disturbances in patients admitted for acute stroke, but even less on personality changes secondary to stroke. Personality changes after stroke are frequent psychiatric disturbances observed and reported by the caregiver or by the clinician, and sometimes by the patients themselves [8]. Personality Change Due to Stroke-Apathetic Type (Post-stroke Apathy) as a neurobehavioral disturbance secondary to stroke, restrains the ability of the patient to return to their previous occupational and social activities and it may be associated with executive functioning impairment [9-12]. Apathetic patients often present neuropsychiatric comorbidity and depression is the most frequent [13]. About 10%-50% [14, 15] of acute apathetic stroke patients and in about 50% of post-stroke apathetic patients [16-18] show depression. This comorbidity may be due to the occurrence of symptom of anhedonia, which is present in the two. Apart from comorbidity between apathy and depression in stroke patients the two may not be statistically associated [14, 18]. Apathetic stroke misdiagnosed as depressive may be prescribed with antidepressants and do not improve as would be expected if they were depressed.

An attempt to better define the relationships between post-stroke apathy, depression and executive functioning (reasoning, attention/speed and motor control, mental flexibility) disturbances is expected to generate a greater knowledge for the detection, prevention, treatment, and prognosis of this condition.

2. DEFINITION OF APATHY, RELATED CONCEPTS AND RELATED SYMPTOMS

Etymologically, apathy is a word with a Latin and a Greek origin. From the Greek “Apátheia” (απάθεια), it means absence of sensibility, indifference, spiritual calm, impassibility, absence of pain. This term used by the school of Hellenistic philosophy in the old Athens-Greece had the meaning of indifference for what one was not responsible for. From the Latin “Apathia”, apathy is composed by “a” plus “pathos”, and corresponds to an absence of passion, calm, insensibility of the soul [19]. Apathy is an insensibility to suffering, an absence of any kind of emotion, i.e. a lack of interest in or concern for things that others find moving or exciting [19].

The clinical diagnosis of apathy comprises other neuropsychiatric symptoms, or behavioural disorders [27] such as abulia, athymormia, anhedonia and/or emotional indifference [20, 21, 28-31].

Abulia, from the Greek “αβουλία” means non-will. Abulia as a lack of willing is expressed by an absence or reduction of spontaneous acting and thinking secondary to a neurological disease [21, 29-31]. In APA’s dictionary [6] abulia is described as an “extreme loss of initiative and drive, resulting in an inability to make decisions or initiate voluntary actions” which may be seen in individuals with acquired brain damage, or schizophrenia or other primary brain lesions. Ribot [32] defined abulia as ‘‘loss, lack or impairment of the power of the will to execute what is in mind’’. Abulia is not the result of ‘‘lack of desire’’ but a consequence of abnormalities in ‘‘the transition from motive and desire, to execution’’ [32]. Poverty of behaviour and speech, lack of initiative, loss of emotional responses, psychomotor slowing and prolonged speech latency express abulia [33, 34]. In neurosciences and clinical neurology, abulia is defined as a: (1) difficulty to initiate and sustain purposeful movements; (2) poverty of spontaneous movements; (3) reduced spontaneous speech; (4) increased response time to queries; (5) passivity; (6) reduced emotional responsiveness and spontaneity; (7) reduced social interaction; and (8) reduced interest in usual pastimes [29, 31].

Anhedonia from the Greek “αν” (without) plus “ηδονή” (pleasure) [http://www.thefreedictionary.com/anhedonia] describes the lack of pleasure or interest in activities that the patient once enjoyed. It is the “inability to enjoy experiences or activities that would normally be pleasurable” [6].

Avolition comes from “a” plus “volition”. Avolition is a “failure to engage in goal-directed behaviour” [6]. Clinically, patients with avolition present an inability to start and

maintain a specific goal-direct activity [29, 30], which is included in a wide concept of apathy.

Athymormia defines a loss of psychic, motor or affective auto-activation. Individuals are able to be hetero-activated (activated by others), but not activated by their own will (Self-activated) [21, 29-31, 35].

Finally, emotional indifference represents a lack of emotions that usually arouse an individual [12, 21, 29, 30, 36].

What characterizes an apathetic state is the inability of an organism to be motivated, to be aroused, or to be activated by any external or internal stimulus and consequently the inability to react emotionally or by motion [20, 21].

As defined in the American Psychological Association Dictionary of Psychology [6], motivation is “the process of starting, directing and maintaining physical and psychological activities” and “includes mechanisms involved in preferences for one activity over another and the vigour and persistence of responses” [6]. The absence of motivation defines the presence of apathy. Motivation is a concept that incorporates others concepts (Impetus, drive, need, motive, will, volition), which in some theories substitute the concept of motivation. We think that these concepts are different but, at the same time, they are present in and are part of the concept of motivation. Impetus or drive is a “generalized state of readiness precipitating or motivating an activity or course of action”. Drive is usually “created by deprivation of a needed substance, the presence of negative stimuli or the occurrence of negative events” [6] either from the environment or from the organism itself. Need is a “condition of tension in an organism resulting from deprivation of something required for survival, well-being or personal fulfilment” [6]. Motive is a “specific physiological or psychological state of arousal that directs an organism’s energies towards a goal”. Will is the “capacity by which human beings are able to make choices and determine their own behaviour in spite of the influences external to them” [6] being fundamental for motivation and subsequent behaviour. Volition is a cognitive process, a “faculty by which an individual decides upon and commits to a particular course of action, especially when this occurs without direct external influence… includes choice and decision, self-control, intentional action and an active rather than passive response to events” [6].

Motivation is distinct from emotion, which is “a complex reaction pattern involving experiential, behavioural and physiological elements, by which the individual attempts to

deal with a personality significant matter or event" [6]. An emotion is determined by the specificity and significance of the event.

Behaviour corresponds to "actions by which an organism adjusts to its environment". Action, as part of behaviour, is a "self-initiated sequence of movements, usually with respect to some goal" [6]. Lack of motivation often results in an absence of any goal-directed or any other type of physical activity [22]. Sometimes, actions or emotions may not be triggered by the subject himself but are prompted by others, who represent a motivational external stimulus for action.

Motivational behaviour, as a complex pattern of action, is a response to either physiological or acquired needs influenced by genetic and/or environmental factors. The concept of impetus/drive involves the energy that, underlying motivation, leads to the satisfaction of primary needs or of other learned needs. As an example, the impetus for eat, added by a need to sustain the organism alive through the act of eating, is felt by the organism through an internal perceptive system as deprivation/unpleasant feeling. This deprivation would lead to behaviour of searching food and eating to satisfy the need. The organism feels this satisfaction as a "pleasant feeling". Organically speaking, the satisfaction gives a homeostatic stability to the organism. Intellectual needs, such as curiosity, are secondary needs but, as the primary needs, they are percept, or felt by the organism, and interpreted as any other need (a secondary one). Curiosity is a strong need or motivation for knowledge, it is a powerful impulse originated by a feeling of deprivation (the curiosity itself), which provokes an exploring behaviour whose goal is to get any kind of knowledge and the consequent feeling of pleasure.

Motivational behaviour includes all kind of activities related to the acquisition of a group of information about environment, ultimately of importance for the survival of the organism. Motivations secondary to other primary motivations are a consequence of a wish or a will resulting from a state of need (or homeostatic instability). [23-26]

2.1. The Concept of Personality and Personality Change after stroke

Personality is "the unique psychological quality of an individual that influence a variety of characteristic behaviour patterns (both overt and covert) across different situations and over time" [6].

A personality change is a “chronic, inflexible, maladaptative pattern of perceiving, thinking and behaving” [6]. A personality change defines a pattern of inner experience and behaviour that deviates from the expectations of the culture of an individual. It is stable over time and impairs the ability of the individual to function in social or other settings [30, 36].

The patient with a personality change has difficulties in adjusting to new circumstances. Avoiding new experiences and adopting an unvarying routine are possible and usual reactions of those patients who are responsiveness and show apathy. Confrontations with a task or social demands do not trigger the patient and yet patients are affable and agreeable when left in peace. Later, changes in emotional state may become more obvious with irritability or stereotyped and inflexible emotional reactions.

These changes may be evident for some time, hindering rehabilitation and providing a considerable burden for relatives. The perception that the carer has about the status of the stroke patient is described as dissatisfaction, unenergetic and easy-going. These may be classified by the carer either as negative or as positive, probably depending on what was the personality of the patient before stroke [37].

Apathetic status due to stroke, can only be classified as a “*Personality Change Due to a General Medical Condition”* from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [36].

2.2. The Concept of Apathy in Clinical Practice

Apathy defines an absence of motivation and interests, an absence of emotions and a decrease on spontaneous behaviour [21]. A sub-classification of apathy was attempted by Marin RS [22] who described three apathy syndromes, classified based on brain dysfunctions associated to the lack of motivation: 1) Cognitive apathy: motivational disturbance with impairment of executive functions, and related to dysfunction of the fronto-dorso-lateral cortex; 2) Motor apathy: motivational disturbance with extra-pyramidal motor dysfunction, due to an impairment of the motor-striate regions; 3) Sensory apathy: motivational disturbance, which could be manifested also by anosognosia, due to a dysfunction of the right parietal or pre-frontal cortex; 4) Emotional apathy without any of previous associated disturbances, related to dysfunction of neuronal circuits involving amygdala and the cingulum. Mostly in cases of sensory apathy, the apathetic state of the

patient becomes a major problem for himself because the individual is unaware of his real condition and, consequently, of the need for some kind of treatment. [8, 22, 27, 38, 39]

Apathetic patients have difficulties in starting, sustaining goal-direct activity or any kind of voluntary movements. They loose self-activation or self-initiated behaviour [21]. Patients often report “not having plans”, “not caring about things” or having “low interest in doing things”.

In the emotional field, apathetic patients may present indifference, placidity, absence of deep emotions. Occasionally, apathetic patients may show impaired control of the expression of emotions and impulses such as inappropriate desinhibition or aggressiveness. [14, 20, 22, 31, 40-44]

Starkstein and Leentjens [29] proposed an international clinical criteria, for psychiatrists, neurologists, psychologists or other clinical practitioners, which was adapted from Marin et al criteria [20, 21]. The proposal of diagnostic criteria for apathy resumes to: “(A) Lack of motivation relatively to the previous level of functioning of the patient or the standards of his or her age and culture, as indicated either by subjective account or observation by others, (B) Presence for at least 4 weeks during most of the day, of at least one symptom belonging to each of the following three domains: 1) diminished goal directed behaviour, 2) diminished goal directed cognition and 3) diminished concomitants of goal directed behaviour, (C) The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning, (D) The symptoms are not due to diminished level of consciousness or the direct physiological effects of a substance.”

Following the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [36], apathy associated with stroke, is classified as a “*Personality Change Due to a General Medical Condition”* if the predominant feature of the personality change is marked apathy and indifference. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [45] describes apathy as a “*Personality and Behavioural Disorders Due to Brain Disease, Damage and Dysfunction”* in which are affected the I. Expression of emotions and needs, II. Cognitive functioning with disturbance on planning and anticipating personal and social consequences of behavior/absence of behavior, and III. ability to sustain goal-directed activities and emotional behavior.

The DSM-IV-TR [36] criteria of “*Personality Change Due to a General Medical Condition”* apathetic type, is the most suitable to diagnose apathy in the post-acute phase of stroke. However, this criterion is not completely suitable to diagnose apathy in acute phase

of stroke. To diagnose a personality change it is necessary a permanent change of a previous pattern of patients behaviour and cognition, which is not suitable for an “acute phase” of a disease such as stroke.

3. ASSESSMENT OF APATHY

There are several scales or inventories used to assess apathy. In the assessment of apathy, it is of most importance to observe not only motivation but also behaviour, thinking, and emotional response (In Guidelines for Apathy Evaluation Scale provided by Marin RS).

Marin et al [21] developed the 18-item Apathy Evaluation Scale (AES), which is the most used scale in the study of apathy in stroke patients [See [14, 46-48]]. Originally, it aimed at characterizing and quantifying apathy in patients older than 55 years old, based on clinical, self-rated or informant opinion. Factor analysis of AES [21] identified three main factors important in the assessment of apathy: cognitive (items 1, 3, 4, 5, 8, 11, 13 and 16), behavioral (items 2, 6, 9, 10 and 12) and emotional (items 7 and 14).

The AES is the most used scale in the study of apathy in acute stroke and post-stroke patients, which validated our selection of this particular scale. The hypothesis to assess apathy, clinically and self-rated, using the same validated items was a second reason for selection of this scale. The AES was constructed based on Marin et al [21] definition of apathy, This is the same definition that supports several studies, which strongly sustained the use of the AES.

In the study of the metric properties of the AES, for the principal components factor analysis of the AES, Marin et al [21] identified three factors: “General apathy”, “Curiosity or novelty seeking” and “Insight and lack of concern about one’s problems”. Internal consistency was high for the clinical-rated version, with a coefficient α of 0.90, for the self-rated version with a coefficient α of 0.86 and for the informant-rated version with a coefficient α of 0.94. The three versions were moderately-highly correlateed: AES-C/AES-S: r=0.72; AES-C/AES-I: r=0.62; AES-S/AES-I: r=0.43; p-value <0.001.

Clarke et al [47] re-examined the factor structure of the three versions of the AES and calculated cut-off scores for the metric diagnose of apathy. Apart from the English version, AES was also validated in German [48] and in Chinese [46]. For each version on

these two languages, internal consistency (Cronbach α>0.80) was high, giving good metric properties for the use of AES for clinical and research purposes. In this work we aimed at validating the in Portuguese version of the AES [49] (See Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*).

Leuken et al [50] created a 10-item short version of the AES adapted for demented nursing home residents, easier and faster to accomplish and with more acceptance by professional caregivers. The Leuken et al [50] short version of the AES had high internal consistency (short AES clinical-rated version: Cronbach α=0.95; AES self-rated version: Cronbach α =0.92). A cautious reading and interpretation of the 18 items of the AES (Marin et al., 1991) or of the 10 items of a short version of the AES [50] revealed that some are inappropriate to be used in the context of an acute hospital ward. Consequently, Caeiro and Ferro [49] also developed a 10-item version of the AES, to assess apathy in acute stroke units settings. This version also have good construct validity and internal consistency (short AES clinical-rated version: Cronbach α =0.70; Split-half=0.76; short AES self-rated version: Cronbach α =0.65; Split-half=0.57). (See Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*)

Starkstein et al [51] developed the Apathy Scale, which is an adapted version of the AES, validated in patients with Parkinson's disease, but also used in stroke patients. This scale had high internal consistency (Coefficient α=0.76) and good inter-rater reliability (r=0.81, p<0.01),

The Neuropsychiatric Inventory (NPI) is one of the first inventories that assesses neurobehavioral and emotional disturbances secondary to a disease, and includes the assessment of apathy [52]. The NPI is useful if the rating of a caregiver is needed. This maybe a limitation because the caregiver is inapt to assess apathy of the patient in acute settings such as stroke units.

Habib [53] also made a proposal of a questionnaire to assess disorders of action and motivation in neurological practice. Recently Sockeel et al [54] and Dujardin et al [55] developed the Lille Apathy Rating Scale, mostly used for patients with Parkinson disease.

4. THE APATHETIC PATIENT

4.1. Clinical Case 1

A 50 years old male, economist and professor, suffered a first-ever right-sided subcortical ischemic stroke. He had type II diabetes and hypercholesterolemia. There was no history of previous psychiatric or neurological disease. The wife and himself described him as having an anxious and irritable temperament previous to stroke.

He came to the emergency room and his wife described that he had been apathetic and somnolent for the last seven days. During examination he was still presenting these same apathetic symptoms and drowsiness, disorientation, with fluctuations during the day and all over the following week. He had left-sided brachial and facial paresis. CT-scan showed a right-sided anterior thalamic infarct. Transcranial Doppler disclosed a mild left-sided MCA stenosis. Trans-esophagic examination did not show a cardio-embolic source for stroke. While he stayed in the stroke unit no other complications were observed. At discharge he was considered completely recovered without any apparent neurologic sequels (modified Rankin scale score of 1).

He performed a neuropsychiatric and neuropsychological evaluation two weeks after stroke onset. In the observation room, I started to ask him to explain me what happened with him. His first reaction was to look at his caregiver to answerer for him. Then, looked at me and gave a short answer saying that he had a stroke. In the absence of spontaneous speech or complains, I had to ask him direct and simple questions to obtain information directly from him and to assess spontaneous speech. He answered everything with short sentences and, apparently, not revealing intellectual changes.

This short neuropsychiatry and neuropsychological evaluation revealed that he had no language, memory or executive impairments. He described himself as being unmotivated, with low energy and consequently having difficulties in starting, sustaining and finishing any goal-direct activity. He also reported emotional indifference, less concerned about things. He characterized this sate of his as apathetic (Apathy Scale=13 points). At clinical observation we observed all these apathetic characteristics but also athymormia and low initiative (10-item Apathy Evaluation Scale=17 points).

At 8-months after stroke he came for a second neuropsychiatric and neuropsychological evaluation. During the previous seven months his wife described him as a different person not showing his usual irritable or anxious behaviors, without motivation,

initiative or self-activation and presenting emotional indifference. He would do things only if prompted by his wife. He was not showing facial, verbal, or motor reaction of like or dislike. Serotoninergic and noradrenergic antidepressants, bromocriptine and modafinil were tried without effect.

After stroke, this patient was still working, but his days were preferentially spent in from of the TV, changing channels. He told that this was strange because he was not like that before stroke. He also told that he had finished his PhD because he was told to do that and not because he wanted to. He recognized that this state of mind, emotion, volition, was not the usual for a man like he used to be, or for any human being, but he was not able to react emotionally to that fact. He had insight about his present condition, but he really did not care about his personality changes.

The wife told that her husband used to be a fighter, sometimes rude, despotic. Now he was a different man, who accepted everything she tells him to do, not raising his voice and staying at home every possible time. On the extreme of previous personality, now he was unable to do anything unless she asked him to do. She also told that he had to teach, but it was she who usually remembered him that he had to prepare the lesson (which was done long before stroke) and the time of it.

During this second neuropsychiatric and neuropsychological evaluation his facial expression did not show any emotional change and few spontaneous movements were observed. At the beginning, sometimes the patient observed the room probably identifying where he was. The patient answered to every question. Either if the topic of conversation was about something sad or amusing he did not react. I asked him if he had find anything amusing he said that “some things were” but his facial expression did not show any emotional change.

Due to learning effect on neuropsychological tests, and because this patient was told as being someone with high intellectual abilities, we chose not to evaluate with the same neuropsychological test that we had use 7 months before.

The results on this 8-months neuropsychological evaluation revealed a good score in the screening test of MMSE (score=29 points). He showed impairments on sustained attention/speed (Trail Making A and B) and motor control, in concentration (Toulouse Pieron), in verbal initiative (Food, Words stated by P and R), and on “abstract behaviour” and “shift of set” (Wisconsin Card Sorting Test). He continue to describe himself as being apathetic (Apathy Scale=28 points), that is unmotivated, without interest in things that usual

aroused him, having difficulties in starting, sustaining and finishing any goal-direct activity but able to be activated if prompt by his wife, and emotional indifferent. His wife described these same apathetic characteristics but in a severer degree than the patients (18-items Apathy Evaluation Scale score=49 points). At clinical observation he was apathetic (18-item Apathy Evaluation Scale=48 points).

This example is an extreme form of post-stroke apathy. Most of the apathetic patients have some difficulties in starting and sustaining goal-direct activity and self-initiated behaviour as we said before. Apathetic patients rarely show verbal or motor initiative. Once they think that had answered or done the task they stop their activity (sometimes without ending the task). Thoughts related to tasks are rare, but other times if asked about what they were thinking they might say, shortly, what was about. If asked if they do things, some patients report the simple short answer “no”, others may answer that they “did not remember to think or do”.

4.2. Clinical Case 2

A 60 years old male, journalist, suffered two strokes. The first stroke was a right-sided thalamic hemorrhage and the second was a left-sided ischemia at the anterior nucleus of the thalamus. He was a healthy man with a non-identified hypertension. There was no history of previous psychiatric or neurological disease. He was a smoker of 40 units a day. Two years before, he had a facial left-sided hemiparesis.

Fifteen days before the first stroke onset he started to present apathy and a change in daily routine behaviors, he was speechless, and he had urinary incontinence, diarrhea and vomiting. At this first episode of stroke, when arrived at the hospital he had left-sided facial paresis, he was apathetic, bradypsychic, drowsiness and present temporal disorientation. MR-scan with diffusion showed a right-sided thalamic hemorrhage probably caused by multiple intracerebral cavernoma. At discharge he was almost recovered without any apparent neurologic sequels but remaining apathetic and with bradypsychia (modified Rankin scale score of 2). He had a second stroke 12-months after. At onset of this stroke he presented memory disturbances, anosognosia and enurese. MR-scan with diffusion showed a left-sided ischemia at the anterior nuclei of the thalamus. Carotid triplex disclosed a mild bilateral calcification. At discharge he had a mild impairment for daily activities (modified Rankin scale score of 3).

The patient performed two neuropsychological/neuropsychiatric evaluations. The first was 8-months after stroke and the second 14-months after stroke. In the first evaluation it was detected abnormal fluency of spontaneous speech, temporal disorientation and difficulties in planning a drawing. No impairments were found in attention (Letter cancelation Z-score=1.95), sustained attention/speed and motor control (Trail Making A Z-score=0.84), verbal immediate recall (logic memory Z-score=0.79; verbal working memory Z-score=-0.15; verbal associative learning Z-score=1.22), verbal long-term recall (logic memory Z-score=-0.68; verbal associative learning Z-score=-1.49), visual immediate recall (visual memory Z-score=-0.07), verbal fluency (Semantic initiative Z-score=0.28), repetitive sequential patterns (Motor sequence Z-score=0.44; Graphic sequence Z-score=0.67), mental flexibility (Trail Making B Z-score=-0.43), in abstract reasoning (Raven Ab non-verbal Z-score=-0.53; Verbal proverbs Z-score=-1.11). Clinically he was scored as apathetic (18-item Apathy Evaluation Scale=51 points; Z-score=5.45). He was mildly depressed (MADRS score=23) and he was independent for daily activities (IADL Z-score=0).

His apathetic condition remained stable over the following months until the second neuropsychological and neuropsychiatric evaluation. At this evaluation the patient presented atimormia in spontaneous speech but also impairments in temporal and personal orientation (Z-score=-16.97), verbal immediate working memory (Z-score=2.53), verbal long-term recall (verbal associative learning Z-score=-15.28), mental flexibility (Trail Making B Z-score>3.00). No impairment were found in language (Nomination of object (Z-score=0.0), nomination of colors (Z-score=0.0), repetition (Z-score=0.0) and comprehension (Z-score=0.42)), attention (Letter cancelation Z-score=1.17), sustained attention/speed and motor control (Trail Making A Z-score=-0.22), verbal immediate recall (logic memory Z-score=1.06; verbal associative learning Z-score=-1.36), verbal long-term recall (logic memory Z-score=2.32), visual immediate recall (visual memory Z-score=-1.22), verbal fluency (Semantic initiative Z-score=-0.74), repetitive sequential patterns (Motor sequence Z-score=0.44; Graphic sequence Z-score=0.66), in abstract reasoning (Raven Ab non-verbal Z-score=-1.27; Verbal proverbs Z-score=-1.11). He scored himself as being apathetic (18-items Apathy Evaluation Scale score=44 points; Z-score=2.92), and clinically he was scored as apathetic (18-item Apathy Evaluation Scale=45 points; Z-score=4.27). He was mildly depressed (MADRS score=14) and he was mildly dependent for daily activities (IADL Z-score=-1.50).

Serotoninergic antidepressant (Sertraline) was tried without effect.

4.3. Clinical Case 3

A previously independent 62 years-old women, married, with 4 years of education, with hypertension and diabetes, was admitted because of drowsiness and speech disturbances. CT-scan and MRI disclosed bilateral mesial thalamic infarcts. A MR was performed 5-months later and showed ischemic lesions affecting the right-sided corona radiata, right-sided posterior thalamo-capsular areas, and bilateral thalamic lacunes.

During the first month follow-up, she improved from physical squeal of stroke and calmly she started to do her daily activities by herself.

Five months after the patient came for a neuropsychological and neuropsychiatric evaluation. She was abulic, and she would not speak or move unless prompted to do so. At this time, she was dependent for all daily activities, except for her hygiene, dressing or eating.

During this evaluation the patient presented atimormia. Spontaneous language was not fluent was also interrupt by anomic pauses. She showed impairments in temporal, space and personal orientation (Z-score=-20.41), reading (Z-score=-10.0), attention (Letter cancelation Z-score=-7.40. She stopped thinking it was finished), calculation (Z-score=-2.05), verbal immediate working memory (Z-score=-3.72), verbal immediate associative recall (Z-score=-2.65), verbal long-term recall (verbal associative learning Z-score=-11.53; verbal logic memory Z-score=-2.35), verbal fluency (Semantic initiative Z-score=-4.51), repetitive sequential patterns (Motor sequence Z-score=-4.69), and in abstract reasoning (Raven Ab non-verbal Z-score<-4; Verbal proverbs Z-score=-4.45). No impairment were found in language (Nomination of object (Z-score=0.0), nomination of colors (Z-score=0.0), repetition (Z-score=0.0) and comprehension (Z-score=0.42)), verbal immediate logic recall (Z-score=-1.11). She did not score herself as being apathetic (18-items Apathy Evaluation Scale score=25 points; Z-score=0.25), but clinically she was as apathetic (18-item Apathy Evaluation Scale=56 points; Z-score=5.45), and the relative also identified apathy (18-item Apathy Evaluation Scale=54 points). She was not depressed (MADRS score=0).

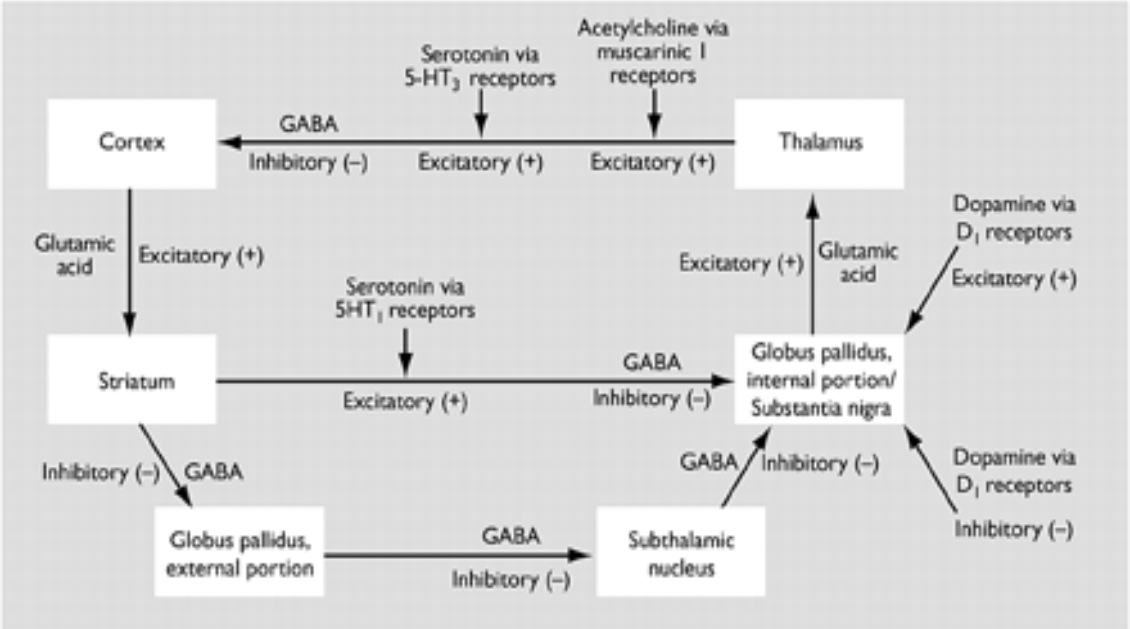
This patient is an example of how dementia and apathy are associated. It is not specific if apathy was a first sign of the beginning of a vascular dementia or if it was the vascular dementia that prompt apathetic symptoms.

A serotoninergic (Fluoxetina) and a dopaminergic agonist (Ropinirol) were tried without significant effect.

5. PATHOPHYSIOLOGY OF MOTIVATION AND OF APATHY

Our knowledge about the pathophysiology of apathy is still insufficient. Apathy is, sometimes, related to cognition or linked to emotions [56], and other times reported as a personality disturbance secondary to a frontal lobe lesion [57]. Decreased dopaminergic activity is a main neurochemical correlate as is seen in Parkinson's disease or in schizophrenia. Increase of serotoninergic activity, especially in older patients, can also trigger apathy [58-64].

Figure 1. "Anatomical organization, internal neurochemistry, and known external neurochemical modulators of the fronto-subcortical circuit" (From Lyketsos et al. [65])



The complexity of behaviours triggered by motivation, either we think about actions sustained on previous experiences or about reflexive behaviour, involves the coordination of different neuronal levels, which could include the neocortex, the limbic system, or centres like the hypothalamus and the brainstem [23, 59].

Motivational disturbances such as apathy, lack of spontaneity and indifference, with loss of motor and affective initiative may occur after several types and locations of brain lesions (uni or bilateral). These lesions may involve the caudate, internal globus pallidus, putamen or a part of a wide circuit (the motivational circuit) that includes the medial nucleus of the thalamus and certain frontal regions connected with the limbic system such as the anterior part of the cingulate gyrus [12, 35, 44, 53, 58, 59, 66-68]. Reports of patients with so called “frontal lobe syndrome” with apathetic characteristics, secondary to bilateral lesion of both globus pallidus (motor/self activation) and of both caudate nucleus (motivation/apathy), suggest that these two brain structures are part of a network, connected with the frontal cortex, essential for organization of motivational behaviour [35, 57, 66].

Apathy due to damage of the projections from the globus pallidus to the nigro-striatum dopaminergic area or lesions of several mesencephalon nuclei disturbs locomotor goal-direct behaviour [15, 43] (Figure 1). Thalamus-cortical fibres cross through the genu of internal capsule, coming from the ventral anterior and medial dorsal nucleus of the thalamus, and ending in the anterior area of the frontal lobe. Mal-functioning of thalamic projections disturbs the normal activity of the ipsilateral frontal cortex [31, 69]. The caudate nucleus is important for spontaneous activity, as a prefrontal activity regulator [66]. Caudate nucleus and thalamus have limbic afferents from the amygdala and orbital gyrus (inferior or orbital surface of the frontal lobe), coding the emotional meaning of the events. It is known the influence of the limbic signals into the striate-thalamic-cortical circuits, and consequently in motor or cognitive inhibition, in neurologic and psychiatric diseases such as depression or in apathy secondary to a medical condition [67, 70, 71].

Right-sided lateralization of brain lesion is of major importance for patients who present apathy. Davidson [72] suggested that the anterior regions of the left and right hemisphere are specialized in the process of approach and withdrawal, respectively. Thus, patients with a right-sided lesion may experience a loss of interest and pleasure in being with people and experience a psychomotor retardation. Hypoactivity in the left-sided frontal area is associated with emotions and related to reduction on approaching behaviours such sadness and depressive mood [72] but not necessarily with a total withdrawal.

The frontal network comprises five circuits, three neurobehavioral (dorsolateral, orbitofrontal and anterior cingulate) and two motor (oculomotor and motor) [73]. The anterior cingulate circuit is the most important cortico-subcortical circuit for motivation, whose damage is responsible for apathetic states after neurological conditions including stroke.

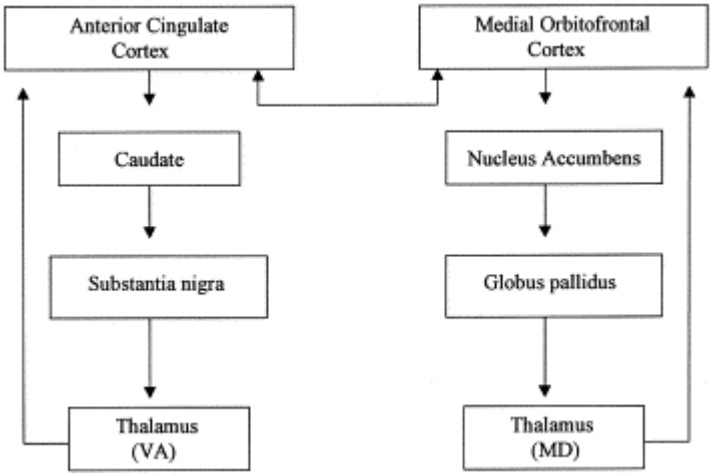
In reality, there are two anterior cingulate circuits: one direct and one indirect [74, 75] and both start in (A) a cortical area, the Anterior Cingulate Cortex (Area 24). Other cortico-subcortical areas are involved and linked to the Anterior Cingulate Cortex: Parahippocampal gyrus (Includes the entorhinal cortex (area 28; this area gives emotional information about the stimulus) and perirhinal cortex (area 35)), Orbitofrontal cortex (Area 12; this area gives emotional information about the stimulus), Amygdala (Connects the limbic system with the anterior cingulate circuit), Intralaminar nucleus (At thalamus, is connected with the reticular formation in the brainstem, and indirectly allows the cortex to be involved in the regulation of the sleep-wake cycle), Raphe nuclei (Located in the brainstem, their main function is to release serotonin to the rest of the brain. Selective serotonin reuptake inhibitors antidepressants act in these nuclei), Tegmentum (Located inside the brainstem, comprises mesencephalon/midbrain. This multi-synaptic network of neurons is involved in many unconscious homeostatic and reflexive pathways).

These areas project to (B) the Ventral Striatum/Nucleus Accumbens, which includes the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle (The limbic striatum).

From the Ventral Striatum/Nucleus Accumbens go projections to the (C) Globus Pallidus. The Globus pallidus is part of the telencephalon and is associated with functions such as motor control and learning. A direct pathway connecting the Striatum and the Globus Pallidus interna/Substantia Nigra complex, and an indirect pathway linking Striatum to Globus Pallidus externa, then to subthalamic nucleus and back to Globus Pallidus interna/Substantia Nigra complex. Both direct and indirect circuits modulate input to the thalamus. Direct and indirect pathways modulate circuit activities in response to different inputs. Dysfunction in the direct circuit causes abnormal thalamic inhibition, whereas indirect circuit dysfunction leads to disinhibition and thalamic overactivity. Each set of circuits is present in each hemisphere. [75]

Globus Pallidus projects into the (D) Dorsomedial nucleus of the thalamus, which in turn, and finally, projects to the cortical areas (A) where the circuit started. (Figure 2)

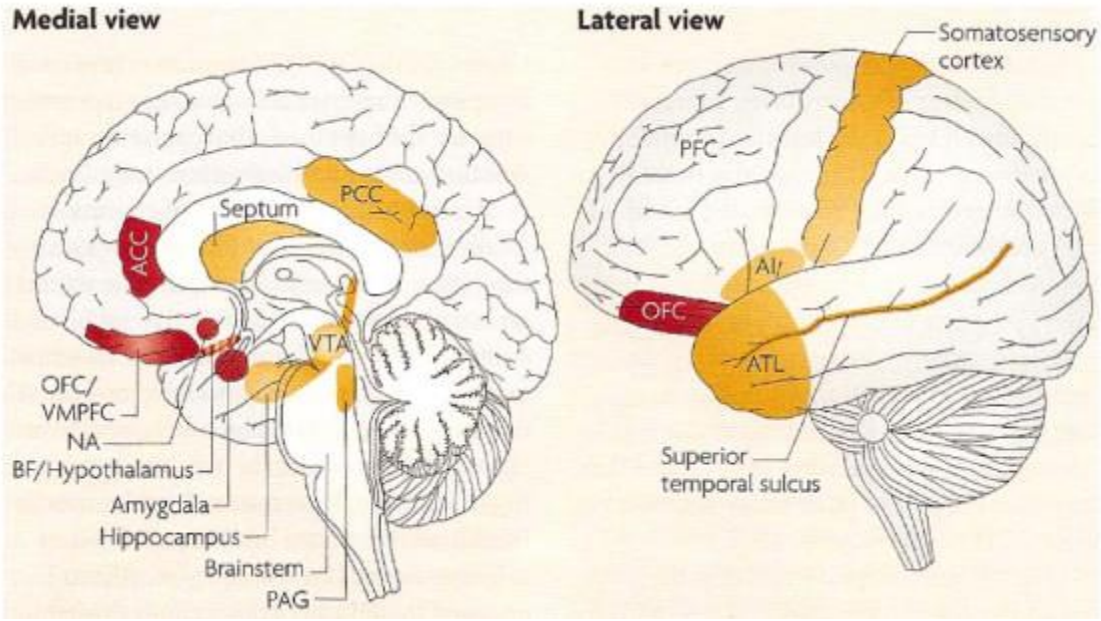
Figure 2. Motivational Circuit (From Tekin and Cummings [75])



The anterior cingulate circuit allows intentional selection of the exterior stimulus, which is sustained by internal needs and by a combination of emotional information with motivation. A lesion in any level of the anterior cingulate circuit (anterior cingulate gyrus, caudate, globus pallidus, thalamus and interconnecting pathways) can be followed by dysfunctions such as apathy, abulia, loss of psychic self-activation or even akinetic mutism and catatonia [74].

Limbic areas have also major importance for the processes of motivation and apathy (Figure 3). The information from the environment reaches the limbic structures, and to the associated motivational circuit (Figure 2), through the posterior hemispheric systems, where it is translated, recognized and included in the pre-existing supports [22]. The posterior systems provide a representation of the environment, which is incorporated in the anterior areas of the temporal lobe and in the insula.

Figure 3. Emotional Brain (From Hoffmann et al. [76])



Emotional Brain: Core (red colored) and Extended dealing with brain (orange colored) regions. (Reproduced with permission Nature Publishing Group). Core Emotional brain. OFC: orbitofrontal cortex. VMPFC: ventromedial prefrontal cortex. ACC: anterior cingulate cortex. BF: basal forebrain. NA: nucleus accumbens. Extended Emotional Brain. PAG: periacqueductal gray matter. ATL: anterior temporal lobe. AI: anterior insula. PCC: posterior cingulate cortex. VTA: ventral tegmental area.

5.1. Location of Lesions Causing Apathy in Stroke Patients

Cases of apathy secondary to focal and circumscribed stroke lesions helped the study of the anatomical basis of apathy.

Apathy may be associated with infarcts at paramedian diencephalon-mesencephalon [59, 66, 77, 78]. Lesions in the medial reticular activating system, which is composed by pathways originating in the upper brainstem reticular core that project through synaptic relays in the intralaminar thalamic nuclei to the cerebral cortex, are also a cause for apathy [79].

A review from Jorge and colleagues [58], based on the findings from 5 studies, suggested that stroke involving subcortical areas of the cortico-subcortical circuits is associated with apathy. Apathy secondary to subcortical stroke lesions may be due to indirect dysfunction of the frontal lobe. The most commonly subcortical stroke lesions causing apathy are located in the cingulate gyrus [80], the posterior limb of the internal capsule [12], the lenticular nucleus or the globus pallidus, and the anterior and medial thalamic nucleus [31, 69].

Two studies on apathy in acute stroke provided information [14, 15] about patients with haemorrhagic stroke type. These patients have a slight higher risk to present apathy compared with ischemic stroke patients. In these studies, apathy is not associated with stroke location. Incidence of apathy in acute stroke [10, 14, 15, 80, 81] is comparable in patients with left or right-sided hemispheric lesions.

Right-sided stroke lesions involving fronto-subcortical circuits or cortico-limbic-reticular subsystems, encompassing the frontal region [80, 82-84], anterior cingulated gyrus [80], basal ganglia, anterior limb of the internal capsule [12], the lenticular nucleus or the globus pallidus, the anterior and medial thalamic nucleus [31, 42, 69, 85] cause apathy [8, 18, 74, 86] or indifference [87].

Patients with bilateral lesions or with left-sided stroke lesions at the corpus callosum and cingulate gyrus or at the superior frontal lobe area and basal ganglia, may present hypobulia or apathy or indifference [16, 80, 88, 89] or profound behaviour changes such as athymormia [56].

To identify possible silent ischemic brain lesions is important if apathetic behavioural disturbances appears on community-dwelling elderly subjects. Deep white matter lesions are independently associated with apathy in elderly patients [90].

CADASIL (cerebral autossomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a genetic model of pure subcortical ischemic vascular pathology, often silent until the occurrence of a behavioural disruption needing neurological care. In CADASIL, apathy is common affecting 37.8% to 41% of the patients [91, 92]. The presence of white matter and lacunar lesions [92] and reduction cortical surface volume at the mediofrontal and orbitofrontal areas [91] are independently associated with apathy.

In subarachnoid haemorrhage (SAH) blood invades not only the cisterns, but can also invade cerebral tissue. Neuropsychiatric disturbances are, occasionally, the first sign. In the acute phase of subarachnoid hemorrhage (SAH), 42.4 % of the patients can be

apathetic [93]. Apathy is present in 22% of the patients with perimesencephalic SAH and in 61.5% of the patients with anterior communicating artery **(**ACoA) aneurysms [93]. Higher haematic densities in the left and in the right lateral ventricles are associated with apathy. Lateral ventricles are borderline with subcortical structures linked to anterior cingulate circuit. Apathy is also one of the possible behavioural sequelae of ACoA rupture, although in some systematic studies no cases of apathy were found among SAH survivors [94]. A study with patients with ACoA and MCA aneurysm found abnormal decision-making behaviour (altered sensitivity to both reward and punishment, and impulsive responding) in SAH survivors, which may contribute to difficulties in daily living resulting from apathy [95].

Apathy has also been reported after cerebral venous sinus thrombosis, in cases with thrombosis of the deep venous system and thalamic infarcts or in patients with superior sagittal sinus thrombosis and cingulated infarcts [96-98]. In these cases, the blood clot occurring inside a blood vessel also bounders or invades anterior cingulated circuit structures.

Transient ischemic attack is not a frequent cause for apathy. Sachdev et al [99] studied patients who suffered a stroke or a transient ischemic attack and compared apathetic with non-apathetic patients and the subgroups did not differ in their amygdala volumes.

5.1.1. Evidence from Lesion Studies: Apathy in Acute Stroke

Apathy in acute stroke is associated with stroke lesions involving the posterior limb of the internal capsule [15], caudate or putamen [22], but also with lesions in the territories supplied by the anterior cerebral artery [80] or the internal carotid artery [100]. Right hemispherical stroke lesions are commonly reported and increase the risk of apathy in acute stroke, mostly if the lesion is striatocapsular or thalamic [14, 82] (Figure 4 and Figure 5. Brodaty et al [82] corroborated the association between apathy and right stroke lesions but also reported an association with bilateral stroke lesions. From a study with acute stroke patients [14], of those acute apathetic patients with subcortical stroke lesions, 13% had right sided striatocapsular and 6% had right thalamic lesions.

Figure 4. Right-sided corona radiata, bilateral thalamus (Clinical Case 3)

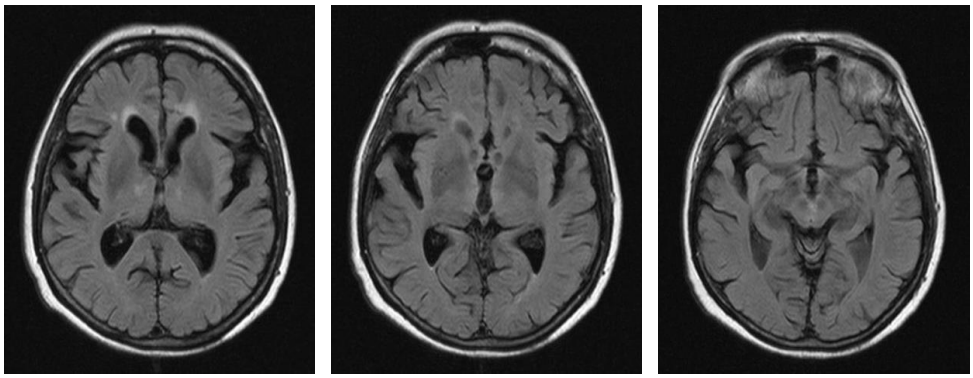
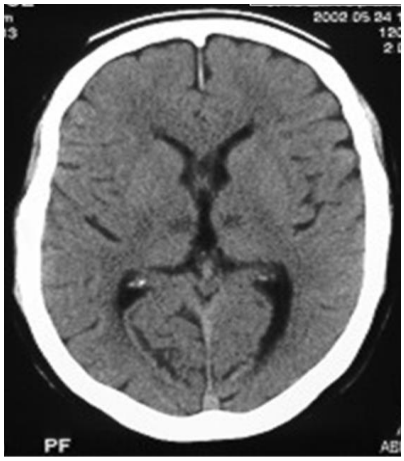


Figure 5. Bi-thalamic infarct



5.1.2. Evidence from Lesion Studies: Post-Stroke Apathy

Post-stroke apathy associated with subcortical brain lesions has been often reported, mostly if they involve the thalamus [85] or the striatum, globus pallidus, substantia nigra and the subthalamic nucleus [16, 88, 89]. Single infarcts or haemorrhages in strategic subcortical locations interfere with specific circuits that link the prefrontal cortex to basal

nucleus or with non-specific thalamic-cortical projections [83, 101-104]. Thalamic-cortical fibres cross through the genu of internal capsule, coming from the ventral anterior and medial dorsal nucleus of the thalamus, and ending in the anterior area of the frontal lobe.

5.2. Evidence from functional studies

Case-studies of post-stroke apathy using brain Single-Photon Emission Computed Tomography (SPECT) are rare but the findings are interesting.

A case study using brain SPECT [68] described a patient presenting psychosis and apathetic behaviour after an acute bilateral thalamic infarct. SPECT showed bilateral hypoperfusion of the frontal lobes, which highlighted the role of thalamo-frontal circuits in the pathogenesis of apathy. Onoda et al [88] using brain SPECT gave further evidence that hypoperfusion of the basal ganglia was associated to post-stroke apathy. Habib [66] reported a patient with an infarct involving the head of the caudate nucleus. SPECT demonstrated an area of decreased perfusion in the right basal ganglia. In patients with bilateral globus pallidus lesions, the lost of self-activation is associated with low activation of the frontal lobe. Both the striate and globus pallidus receive afferents from amygdala, which is involved in the emotional labelling of sensorial stimuli, and from the parahippocampal gyrus. In turn, they (Including the perirhinal and entorhinal cortices, this area is responsible for comparisons of the new information with the one that is already registed) project to the remaining basal nucleus involved in the starting and organization of motor actions. The striate and the ventral globus pallidus are an interface between motivation and action, that is, they are the brain areas where motivations are translated into behaviours and thus are an interface between motivation and action [66]. Yamagata et al [84] study provided further neurophysiological (Event-Related Evoked Potential) evidence of dysfunction of the frontal-subcortical system in apathetic patients with subcortical stroke. The apathetic group of stroke patients showed: (1) prolonged latency of the novelty P3; (2) reduced novelty P3 amplitude over the frontal site, resulting in posterior shift of the scalp topography; and (3) correlations between the changes in novelty P3 measures and degree of apathy state.

Recently, Glodzik-Sobanska et al [83] examined proton MRI spectroscopy findings in unaffected frontal lobes of stroke patients and demonstrated a correlation between apathy and reduction in the N-acetylaspartate/creatine ratio in the right frontal lobe.

In dementia, personality disturbances including apathy are associated with hypoperfusion and hypometabolism, mostly in the frontal cortical areas [102, 105].

6. RATE OF APATHY IN STROKE PATIENTS

Several studies on apathy secondary to stroke, either after focal or extent stroke lesions, account a total incidence range between 15.2% to 91.7%.

6.1. Rate of Apathy in the Acute Phase of Stroke (Apathy in Acute Stroke)

In most of the studies with acute stroke patients, an operational diagnosis of apathy comprises abulia or avolition, athymormia, and/or emotional indifference [20, 28]. There is no nosological definition for apathetic syndromes either in the DSM-IV-TR or in the ICD-10 to be used in the acute phase of stroke [29, 36, 45].

Recent studies reported a frequency of a fifth to a third of cases of apathy in acute stroke [89]. Overall, 15.2% up to 71% of acute stroke patients become apathetic [14, 15, 88, 100, 106, 107]. Apathetic patients are predominantly older, with low educational level, present neglect, have a right-sided hemispherical lesion, and have a greater degree of physical, cognitive, and disturbances in their emotional state (depressed mood).

6.2. Rate of Apathy in the Post-Acute Phase of Stroke (Post-Stroke Apathy)

Studies on post-stroke apathy may be supported by nosological criteria as defined in the DSM-IV-TR [36] or by ICD-10 [45]. However, these criteria do not give specific guidelines, thus most of the studies adopt the criteria of cut-off point of the scale used to assess apathy.

The frequency of apathetic patients in post-stroke phase of stroke range is 20.1% to 91.7% [16, 18, 82, 84-86, 88, 89, 108, 109].

Older age and cognitive impairment are factors associated with post-stroke apathy [82, 88, 89, 108, 110, 111].

7. RISK FACTORS AND ASSOCIATED CONDITIONS FOR APATHY IN STROKE PATIENTS

Several publications suggested that aging increases the risk of apathy in stroke patients [14, 15, 18, 82-84, 88, 89, 108, 110]. Other demographic factors such as male gender and low educational level or social condition were also been pointed as risk factors for post-stroke apathy, although of less significance than age [14, 112].

The presence of cognitive impairment before stroke is a risk factor for post-stroke apathy [82, 84]. Post-stroke cognitive impairment seems to be an important factor associated with post-stroke apathy [82, 88, 89, 108, 110, 111]. Patients presenting post-stroke apathy often show impairments in verbal fluency tasks [84], but also other executive-type dysfunctions [9-11, 31, 110] including of attention and mental flexibility [56, 57, 81, 110, 113].

A review on apathy following stroke [58], both in acute and post-acute phases of stroke, concluded that apathy is often associated with depression.

In the acute phase of stroke, half of the patients with apathy may also present depression [15], however non-depressive patients can become apathetic [14, 40, 88, 100]. Apathetic acute stroke patients often do not have the emotional experiences of loss [14], and do not feel sad, but may show anhedonia [40, 81], which is a symptom that may be confounded with depressive mood. Apathetic patients often do not complain neither expresses their mood and emotional state [14], in contrast to the behaviour usually displayed by depressed patients. Depressed acute stroke patients feel the emotional experience of loss, they feel and complain about anhedonia, and this knowledge about their own emotional state is a great source of pain and despair.

The relationship between post-stroke apathy and post-stroke depression is frequent. About 14% to 51% of the stroke patients present an overlapping between post-stroke apathy and post-stroke depression [17, 82-84, 88, 110]. However, some publications did not report any association between the two neuropsychiatric disturbances [82, 89], and the evidence is inconsistent. Also in the post-acute phase of stroke, post-stroke apathy is mistaken as a mood disorder; however, the absence of feeling of sorrow or anhedonia characteristics of depression excludes the diagnosis of a Mood Disorder Due to Stroke [36]. These two neuropsychiatric disturbances are linked probably because they share symptoms such as diminishing interest in daily activities. Patients with both apathy and depression after stroke also share common neuropsychological features such as low MMSE scores [110]

and working memory impairment [82]. Specific subcortical stroke locations can induce both apathy and depression [82, 110]. Post-stroke apathy has been linked to right hemispheric subcortical lesions [16, 82, 106] while post-stroke depression has been linked to left anterior lesions in one publication [16].

Denial is one possible reason why apathetic acute stroke patients do not mention their emotional state or show any depressive symptoms [14]. The associated between denial and apathy highlights the possibility that the patient denies acute depressive symptoms, such as sadness and anhedonia [14]. In a recent study from Starkstein et al [114] with Alzheimer's disease patients, anosognosia was a predictor of apathy.

8. ASSOCIATED NEUROPSYCHOLOGICAL DISTURBANCES

Post-stroke apathy is among the most troublesome stroke sequel and may eclipse intellectual deficits [115]. In the elderly the association between apathy and executive dysfunction increases [113]. Either in acute and in post-acute stroke phase, persons with impairment in executive functions have difficulty in initiating activities, in giving immediate responses and in inhibiting impulsive behaviours, which may difficult understanding and applying rehabilitation instructions with effort [116]. Above all, apathetic patients present difficulties in executive tasks related to goal-direct abilities and spontaneous psychomotor initiative. They displayed motor slowness and diminished spontaneous movements, and increasing number of motor and verbal perseverations [10, 31, 116, 117].

In the acute phase of stroke, apathy is associated with global cognitive impairment (Low MMSE scores) [14, 15, 88, 100]. The majority of the patients assessed in the acute phase of stroke have, at least, one cognitive domain disturbed such as memory and executive functions [111, 113, 118].

Patients with post-stroke apathy have worse cognitive performances (Low MMSE scores) than patients without apathy [16, 18, 82, 84, 89, 110, 119]. Apathy, as an inability of the organism to be motivated and to drive acts and relationships, is associated with executive impairments [11, 89]. The most frequent neuropsychological impairments are in the domains of attention and concentration, speed of information processing, working memory and reasoning [82, 110, 119]. These neuropsychological impairments remain even after statistical correction for the presence of depression [82].

Apathy is a predictive factor of vascular dementia [115]. Behavioural symptoms such as apathy in Alzheimer's or vascular dementia are highly frequent [120].

9. OUTCOME OF APATHY IN STROKE PATIENTS

The timing of post-stroke apathy assessment varied across studies from 1-day to 15-months from stroke onset. Three studies report the evolution of apathy secondary to stroke over a year [41, 108, 119] and another account the evolution over a 15-months period [110].

Angelelli et al [41] identified a three time higher risk of development of post-stroke apathy, at 6-months/1-year follow-up in patients presenting post-stroke apathy at 2-month post-stroke. Mayo et al [108] studied a cohort of stroke survivors over a 1-year period and found that 50% stroke patients were apathetic. The extent of apathetic behaviour remained stable over the first year after stroke.

Withall et al [110] followed a sample of stroke patients, 2 to 15 months after stroke. Two months after stroke, 21.7% patients had post-stroke apathy. Of these, at 15-months, 21.7% remained apathetic, 30.4% presented apathy and depression and 43.4% did not present any of these neuropsychiatric disturbances. Logistic regression analysis identified early cognitive impairment as a risk factor for post-stroke apathy.

In conclusion, nearly half of the patients with apathy in the acute phase of stroke remain apathetic. Apathy in the acute phase of stroke is a predictor of long-term post-stroke apathy. Further studies are needed to confirm these findings

10. INFLUENCE OF APATHY IN STROKE OUTCOME

Apathy is a risk factor for pour outcome or recovery after stroke [82, 109] because it may unable the patient to return to their previous occupational and social activities [9-11]. The opposite is also true, the absence of apathy within the first year of post-stroke is a predictor of a favourable outcome following stroke [121].

A previous systematic review including five studies supported the association between apathy secondary to stroke and a lower functional status [58]. Stroke is a component of physical health and impairs psychological health, which has a negative influence in other domains of health [122]. Apathetic patients may be less aware or report fewer complains about their functional loose. Apathy interferes with the ability of stroke patient to seek out rehabilitation services and to carry out rehabilitation exercises [89, 123, 124] or return to social relationships [89, 111].

Patients presenting apathy in acute stroke have a greater degree of cognitive, emotional and physical disturbances [14, 15, 88, 89, 100, 106, 107]. Apathy is a main determinant of longer hospital staying following stroke and of nursing home and hospitalization in demented patients [89, 123-125]. Apathetic patients are less likely to seek out rehabilitation services [89, 123-125]. In cases of patients who seek and do rehabilitation the clinical version of the AES can be used to evaluate success in rehabilitation in stroke patients [126]. Apathy, as an inability of the organism to be motivated and to drive acts and relationships, is associated with executive impairments [11, 89] and ultimately interfere with patient's ability to carry out rehabilitation exercises. Apathy secondary stroke increases the burden of caregivers who may misattribute the pathological loss of drive to laziness or defiance [8, 127].

11. MANAGEMENT OF APATHY

The management of apathy includes pharmacological and non-pharmacological interventions such as behavioural psychotherapy [61].

From the experience of case-study reports, drugs with potential effect in improving apathy include: 1) Dopaminergic agents [128] such as amantadine, dopaminergic agonists (e.g. bromocriptine [61] and ropinirole [129]); 2) Stimulants, such as methylphenidate [130] and modafinil [131], because of its effect on stimulation of dopamine and norepinephrine release; 3) Antidepressants with dopaminergic (e.g. brupopion) or noradrenergic (e.g. venlafaxine); activity and 4) Acetylcholinesterase inhibitors (e.g. donepezil [132]] and nootropics [e.g. nefiracetam [17]).

There are, however, no randomized controlled trials to prove the efficacy and safety of these medications in apathetic stroke patients.

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THE STUDY OF APATHY IN STROKE PATIENTS

RESEARCH PURPOSES AND METHODS

1. RESEARCH PURPOSES

The main purpose of the present study was to identify if apathy in acute stroke is a risk factor for a Personality Disturbance Secondary to Stroke-Apathetic Like (Post-stroke Apathy). A second purpose was to investigate if post-stroke apathy was related to acute stroke lesion, if post-stroke apathy was related to post-stroke depression, cognitive impairment or executive impairment, and if post-stroke apathy was an indicator of poor outcome.

1.1. Preliminary Purpose

Our preliminary purpose was to perform a systematic review on apathy associated with stroke. Consequently, we aimed at finding which predisposing and precipitating factors were associated with apathy secondary to stroke (in particular in post-stroke phase), the consequences of post-stroke apathy in patients' life, and which were the unsettled issues on the subject of apathy secondary to stroke. (Chapter 3: Apathy Secondary to Stroke: *A Systematic Review on Apathy Secondary to Stroke*)

For the study of the frequencies and related factors of Personality Disturbance Secondary to Stroke-Apathetic Like we had to validate an apathy scale in Portuguese. Thus, we also aimed at making the description of the metric properties of the Apathy Evaluation Scale (AES), in a voluntary Portuguese sample in comparison with two clinical samples presenting depression and dementia. (Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*)

1.2. Goals: Research Questions

1. To describe the frequencies of Personality Disturbance Secondary to Stroke-Apathetic-Type 1-year after stroke. (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

2. Is acute apathy associated with Personality Disturbance Secondary to Stroke-Apathetic-Like at 1-year follow-up? (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

3. Is Personality Disturbance Secondary to Stroke-Apathetic-Like associated with a specific acute stroke lesion? (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

4. Is Personality Disturbance Secondary to Stroke-Apathetic-Like associated with post-stroke cognitive and executive impairments? (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

5. Is Personality Disturbance Secondary to Stroke-Apathetic-Like associated with post-stroke depression? (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

6. Is Personality Disturbance Secondary to Stroke-Apathetic-Like associated with post-stroke functional outcome? (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

2. SETTINGS

The principal investigator (LC) is attached to the Institute of Molecular Medicine, Unidade Neurológica de Investigação Clínica, of the Faculty of Medicine, University of Lisbon, Portugal.

We conducted the study at the Stroke Unit and the Neurologic Outpatient Clinic, at the Neurology Service, and at the Psychiatric Outpatient Clinic, at the Psychiatry Service, Department of Neurosciences, Hospital de Santa Maria, Lisbon, Portugal.

3. DESIGN

This study was observational, prospective (cohort), descriptive and analytic.

4. SUBJECTS

For the study of Personality Disturbance Secondary to Stroke-Apathetic-Like (post-stroke apathy), we included only stroke patients (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*).

For the study aiming the description of the metric properties of the Apathy Evaluation Scale, we included healthy subjects and a sample of patients with mild Alzheimer's dementia or with mild cognitive impairment, and another sample with diagnosis of major depressive disorder or of a dystimic disorder based on the DSM-IV-TR clinical criteria [1] (Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*).

5. METHODS USED FOR THE RESEARCH ON STROKE PATIENTS

Stroke patients included in this study were consecutive patients admitted to the Stroke Unit of the Neurology Department of a University Hospital. After giving informed consent, stroke patients were assessed at the stroke unit and re-evaluated 1-year post-stroke. Acute examination was performed while patients were in the Stroke Unit (median length of stay 7 days), from day 1 to 10 after stroke onset. Follow-up evaluation was performed 1-year after stroke onset.

Patients were submitted to an acute evaluation, which consisted of: Neurological assessment performed by a neurologist, and Neuro-radiological evaluation (MRI/CT) (details will be described at point 5.1) and a Neuropsychological and Neuropsychiatric evaluation performed by a psychologist (details will be described at point 5.2).

In the acute phase, the psychologist performed a Neuropsychological and Neuropsychiatric evaluation rating apathy, depression, global cognition, executive functions, reasoning, attention/speed and motor control and mental flexibility.

Follow-up assessment consisted of: 1) Neuropsychological and Neuropsychiatric evaluation, 2) Grading of functional disability and 3) Grading perception of health and Quality of Life (Details we will be described at point 5.3.).

5.1. Acute Neurological and Neuro-Radiological Evaluation

Neurological evaluation was performed in the Stroke Unit by the stroke neurologist who was responsible for the patient using the methodology and forms of the Hospital de Santa Maria Stroke Prospective Registry.

Initial stroke severity was graded using the Neurological Institute Health Stroke Scale (NIHSS) [2]. Relevant findings from the neurological evaluation for this study included the Glasgow Coma Scale (GCS) score [3], the presence of hemiparesis and of speech disturbances (items “best language”/aphasia and “dysarthria” of the NIHSS).

The following pre-stroke predisposing conditions for apathy were considered: 1) previous stroke, 2) previous mild cognitive decline, defined as a previous medical diagnosis of mild cognitive impairment, or a history of memory and another cognitive impairment with functional impairment in daily living activities, confirmed by a proxy, and 3) previous alcohol abuse, defined as 5 or more drinks daily, and 4) previous mood or anxiety disorder, if the patient had a previous diagnosis of a mood or anxiety disorder or if the patient had been either prescribed specific medication for these conditions and used it for more than a month.

The neurologist assessed functional outcome at discharge with the modified Rankin Scale (mRS) [4]. An unfavourable outcome was mRS grade of ≥3 (death or dependency).

Neuro-radiological assessment (CT/MRI) was performing during patient hospital admission at the stroke unit.

Based on the acute or on the post-stroke CT-scan and/or on MRI, intracerebral ischemia and intracerebral haematoma were classified as: 1) infratentorial or supratentorial, 2) left or right hemispherical or bilateral, 3) hemispherical cortical or subcortical, 4) hemispherical cortical anterior (frontal lesion) or posterior (non-frontal lesion).

5.2. Acute Neuropsychological and Neuropsychiatric Evaluation

For the past ten years, mental disorders clinical classifications have been evolving towards the creation of systems where operational and empirical diagnostic criteria assure diagnostic reliability and validity (DSM-IV-TR [1] and ICD-10 [5]).

For this project, a group of instruments that allowed psychopathological disorder quantification in all its aspects, together with a strict and unambiguous diagnostic

classification system was used. A psychologist applied all psychometric instruments, following a structured clinical interview. The data emerging from this allowed two diagnostic levels: a descriptive syndromatic and a nosological one [1, 5].

The psychologist assessed apathy and performed the neuropsychological-neuropsychiatric evaluation whenever possible after stroke onset, while in the stroke unit. A psychiatrist also observed the patient if a severe neuropsychiatric disorder was present.

The Apathy Evaluation Scale (AES) [6] was used to assess apathy. The AES, in its clinical (AES-C) and self-rated (AES-S) versions, was validated in a sample of healthy participants, elderly participants, demented patients and depressed patients. Patients were apathetic if scoring above the Portuguese cut-off points in the AES (See Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*) [7].

The Montgomery Åsberg Depression Rating Scale (MADRS) [8] was used to assess depression. Depression was considered if patients reported and displayed depressive mood or anhedonia scoring in the items “Apparent Sadness” and “Reported Sadness”, to assess depressive mood, and “Inability to Feel”, to assess anhedonia, of the MADRS, and if they had a score of ≥7 points in the MADRS [9].

Table 1. Neuropsychiatric and neuropsychological evaluation

	Acute stroke	*1-year post-stroke*
AES-C and AES-S	X	X
MADRS	X	X
MMSE	X	X
Attention/speed and motor control (Trail Making Test A)	X	X
Mental flexibility (Trail Making Test B)	X	X
Verbal initiative (Verbal fluency, Food products)	X	X
Motor initiative (Luria’s alternate hand sequences)	X	X
Graphomotor initiative (Luria’s alternating series)	X	X
Verbal abstract reasoning (Proverbs)	X	X
Non-verbal abstract reasoning (Raven Ab)	X	X
Functional outcome (Barthel index)		X
Quality of life (EuroQol),		X
Self-rated health status perception (EQ-VAS/Health)		X

Abbreviations: AES-C and AES-S: clinical (AES-C) and self-rated (AES-S) versions of the Apathy Evaluation Scale; **MADRS**: Montgomery Åsberg Depression Rating Scale; **MMSE**: Mini Mental State Examination; **EuroQol**: Questionnaire of Quality of Life; **EQ-VAS/Health**: self-rated heath status.

The mini mental state examination (MMSE) [10] was used to assess global cognitive impairment, taking in consideration the Portuguese cut-off points [11].

The neuropsychological assessment was specifically devoted to executive functions, reasoning and attention/speed and motor control and mental flexibility. Executive functions included verbal fluency, motor initiative and graphomotor initiative tests, all included in the Bateria de Lisboa de Avaliação da Demência (BLAD) [12, 13] and some are used in patients with cerebrovascular diseases [14]. Reasoning included verbal [15] and non-verbal [16] reasoning were also evaluated.

5.3. Follow-Up: Neuropsychological and Neuropsychiatric Evaluation

Follow-up evaluation at 1-year post-stroke included all patients assessed previously in the acute phase. The post-stroke assessment included all scales used at acute assessment in order to find the relationship between acute and post-stroke apathy. Thus, at post-stroke we evaluate the presence of a Personality Disturbance Secondary to Stroke-Apathetic Like, depression and cognitive (neuropsychological) impairments. Other scales were included to assess functioning, Quality of Life and perception of health.

The neuropsychological assessment was devoted to attention/speed and motor control, mental flexibility, executive functions, and reasoning. Executive functions included verbal initiative, motor initiative and grapho-motor initiative tests [12-14]. Reasoning included verbal [15] and non-verbal [16] reasoning were also evaluated. Results about the relationship between acute and post-acute neuropsychological evaluation are not present here.

To assess functional outcome or dependency in daily life activities we used the Barthel Index. For Portuguese stroke patients, a total dependency was define if the patient scored 0-8 points, severe dependency was between 9-12 points, moderate dependency was between 13-19 points and independency was for 20 points. For Portuguese subject aging 65 years old or more the mean Barthel Index score is 13.3 (SD=7.6), but the oldest the subject the lowest the score at the Barthel Index (65-75 years old:16.26; 75-84 years old:12.96; ≥85 years old: 9.44) [17-19].

To assess Quality of Life we used the EuroQol, which also includes a self-rated Heath status (EQ VAS) [20-23]. The EuroQol Group [23] made the Portuguese version in 1998, which is widely used in Portugal. The EuroQol is an instrument consisting of five

domains of Health (Mobility, Self-care, Usual activities, Pain/Discomfort, and Anxiety/Depression), each of which is divided into three levels: no problems (1), some or moderate problems (2), and extreme problems (3). The higher score the lower quality of life. EQ-VAS is a self-rated scale to assess Health status using a visual analogue scale, to record the perception of a participant's current overall health. The EQ-VAS is graduated from 0 (the worst health state) to 100 (the best state). We assessed Quality of Life and Health find the relationship of both with post-stroke Personality Disturbance Secondary to Stroke-Apathetic Like.

6. REFERENCES

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Neuropsychiatric Scales and Neuropsychological Tests

ESCALA DE AVALIAÇÃO DA APATIA
Apathy Evaluation Scale

R. S. Marin, R. C. Biedrzycki and S. Firinciogullari. Reliability and Validity of the Apathy Evaluation Scale. Psychiatry Research, 1991; 38: 143-162.

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Pontos de Corte:

EAA - Observação Clínica / AES – Clinical (18 items):

População em geral: 0-9 anos escolaridade: ≥37 pontos

10 anos escolaridade: ≥30 pontos

População em centros de dia: ≥ 22 pontos

EAA - Auto-Avaliação/ AES - Self-Rated (18 items):

População em geral: ≥ 39 pontos

ESCALA DE AVALIAÇÃO DA APATIA

(OBSERVAÇÃO CLÍNICA)

NOME DO DOENTE: _____

IDADE: _____ DATA DA AVALIAÇÃO: _____

Eu vou-lhe perguntar uma série de questões acerca dos seus pensamentos, sentimentos e actividades. Para responder baseie-se nas últimas 4 semanas (1 mês).

Para iniciar fale-me acerca dos seus interesses actuais. Fale-me sobre qualquer coisa que seja do seu interesse, como por ex. hobbies, trabalho; actividades nas quais esteja envolvido ou que gostaria de fazer; interesses que possa ter dentro de casa ou fora dela, sozinho ou acompanhado; interesses que possa não executar, mas que são do seu interesse (ex.: nadar mesmo que seja Inverno).

"Agora gostaria que me contasse a sua rotina diária: Comece desde que acorda e se levanta até ao momento em que se deita."

					Quantificação (1-4)
1.	Ela/Ele está interessada(o) nas coisas	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
2.	Ela/Ele faz coisas durante o dia.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
3.	Começar a fazer coisas é importante para ela/ele.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
4.	Ela/Ele está interessada(o) em ter novas experiências.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
5.	Ela/Ele está interessada(o) em aprender coisas novas.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
6.	Ela/Ele esforça-se pouco nas coisas que faz.	1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico	
7.	Ela/Ele vive a vida com intensidade.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
8.	Acabar uma tarefa é importante para ela/ele.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	
9.	Ela/Ele passa o tempo fazendo coisas que o interessam.	4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico	

10. Alguém tem que lhe dizer o que fazer em cada dia.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

11. Ela/Ele está menos preocupada(o) com os seus problemas do que deveria estar.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

12. Ela/Ele tem amigos.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

13. Estar com amigos é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

14. Quando acontece alguma coisa boa, ela/ele fica emocionada (o).

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

15. Ela/Ele tem compreensão adequada acerca dos seus problemas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

16. Ter as coisas feitas durante o dia é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

17. Ela/Ele tem iniciativa.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

18. Ela/Ele tem motivação.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

TOTAL:

Cotação:

1) Número de interesses manifestos;

2) Grau de detalhes verbalizados, para cada um dos interesses;

3) Aspetos afetivos da expressão verbal e não verbal.

Quantificação:

1- De modo nenhum: 0 itens
2- Minimamente: 1-2 itens
3- Moderadamente: 2-3 itens
4- Muito: 3 ou mais itens.

Referência:

Reliability and Validity of the Apathy Evaluation Scale.

By R. S. Marin, R. C. Biedrzycki and S. Firinciogullari. Psychiatry Research (1991), 38: 143-162.

ESCALA DE AVALIAÇÃO DA APATIA

(AUTO-AVALIAÇÃO)

NOME : _____

IDADE: _____ DATA DA AVALIAÇÃO: _____

INSTRUÇÕES:

Leia atentamente cada uma das seguintes questões.

Em cada uma das questões faça um círculo ao redor do número/frase que corresponde à frase que melhor descreve os seus pensamentos, sentimentos ou acções, durante as últimas 4 semanas.

Quando avaliar "Não é característico" pretende afirmar que não apresenta, que não é característico em si, o que foi descrito ou que o que é descrito não é verdade. Se apresentar essa característica então avalie se está presente "minimamente", "moderadamente" ou "muito".

1. Eu estou interessada(o) nas coisas

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

2. Eu faço coisas durante o dia.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

3. Começar a fazer coisas é importante para mim.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

4. Eu estou interessada(o) em ter novas experiências.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

5. Eu estou interessada(o) em aprender coisas novas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

6. Eu esforço-me pouco nas coisas que faço.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

7. Eu vivo a vida com intensidade.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

8. Acabar uma tarefa é importante para mim.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

9. Eu passo o tempo fazendo coisas que me interessam.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

10. Alguém tem que me dizer o que fazer em cada dia.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

11. Eu estou menos preocupada(o) com os meus problemas do que deveria estar.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

12. Eu tenho amigos.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

13. Estar com amigos é importante para mim.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

14. Quando acontece alguma coisa boa, eu fico emocionada(o).

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

15. Eu tenho compreensão adequada acerca dos meus problemas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

16. Ter as coisas feitas durante o dia é importante para mim.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

17. Eu tenho iniciativa.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

18. Eu tenho motivação.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

MONTGOMERY AND ÅSBERG DEPRESSION RATING SCALE (MADRS)

Nome

Sexo Idade Data

Examinador

INSTRUÇÕES

A avaliação deve basear-se numa entrevista não estruturada. Deve encorajar-se o indivíduo a descrever os sintomas na sua própria linguagem de forma tão detalhada quanto possível. O examinador deve retomar posteriormente os itens que não foram abordados. Perguntas formuladas da forma mais clara e neutra possível devem possibilitar obter as informações que faltam. Se tal não for suficiente para a avaliação pode ser necessário colocar em seguida questões mais precisas. Esta entrevista exige um período mais longo que o dedicado à aplicação da escala o que permitirá ao examinador assegurar-se de que as perguntas são bem compreendidas pelo indivíduo.

O período de tempo levado em consideração para a avaliação dos sintomas relatados pelo doente deve ser standardizado. Para a maior parte dos estudos deve corresponder à sintomatologia do episódio actual – os últimos sete dias - em regra geral.

1 – Tristeza aparente. Corresponde ao desencorajamento, à depressão e ao desespero (mais que um simples desgosto passageiro) que se reflectem no discurso, na mímica e na postura. Cotar em função da profundidade da tristeza e incapacidade para se alegrar, observadas.

0 Sem tristeza.
1
2 Parece desencorajado mas consegue alegrar-se sem dificuldade.
3
4 Parece triste e infeliz a maior parte do tempo.
5
6 Parece infeliz todo o tempo e extremamente desencorajado.

2 - Tristeza manifesta. Corresponde à expressão de um humor depressivo, quer seja evidente ou não. Inclui o desgosto, o desencorajamento ou o sentimento de falta de esperança. Cotar em função da intensidade, da duração ou do grau segundo o qual o humor é influenciado pelos acontecimentos.

0 Tristeza ocasional relacionada com as circunstâncias.
1
2 Triste ou melancólico mas alegra-se sem dificuldades.
3
4 Sentimento dominante de tristeza.
5
6 Tristeza, desespero e desencorajamento permanentes.

3 – Tensão interior. Corresponde aos sentimentos de mal-estar indefinido, de instabilidade, de irritabilidade, de agitação interior, de tensão nervosa no limite do pânico, medo, angústia. Cotar em função da intensidade, da duração ou grau de tranquilização necessária. Distinguir de tristeza (2).

0 Calmo. Tensão interior somente passageira.
1
2 Sentimentos ocasionais de instabilidade e mal-estar indefinido.
3
4 Sentimentos contínuos de tensão interior ou pânico intermitente que o doente só consegue controlar com dificuldade.
5
6 Medo ou angústia sem alívio. Sensação dominante de pânico.

4 – Incapacidade de sentir. Corresponde à expressão subjectiva de uma redução de interesse pelo ambiente circundante ou pelas actividades que normalmente proporcionam prazer. A capacidade de reagir com uma emoção apropriada às circunstâncias ou pessoas encontra-se diminuída.

0 Interesse normal pelo ambiente circundante e pelas pessoas.
1
2 Capacidade reduzida em ter prazer com os interesses habituais (com as actividades usualmente proporcionadoras de prazer).
3
4 Perda de interesse pelo ambiente circundante.

Perda de afecto pelos amigos e pessoas conhecidas.
5
6 Sentimento de estar paralisado emocionalmente, incapacidade de sentir cólera, tristeza, prazer ou incapacidade completa ou mesmo dolorosa de ter qualquer sentimento por parentes próximos ou amigos.

5 – Pensamentos pessimistas.
Correspondem às ideias de culpabilidade, de inferioridade, de auto-acusação, de ter pecado, de remorso e de ruína.

0 Sem pensamentos pessimistas.
1
2Ideias intermitentes de fracasso, de auto-acusação ou auto-desvalorização.
3
4 Auto-acusações persistentes ou ideias de culpa ou pecado definidas mas ainda racionais. Pessimismo crescente relativo ao futuro.
5
6 Ideias delirantes de raiva, de remorso ou de pecado inexpiável. Auto acusações absurdas e irredutíveis.

6 - Ideias de suicídio. Correspondem ao sentimento de que a vida não vale a pena ser vivida, que uma morte natural seria bem vinda, a ideias de suicídio e preparativos de suicídio. As tentativas de suicídio não devem, por si só, influenciar a cotação.

0 Gosto pela vida ou aceitação desta como se apresenta.
1
2 Cansaço de viver, ideias de suicídio apenas passageiras.
3
4 Desejo de estar morto. As ideias de suicídio são comuns e o suicídio é considerado como uma solução possível mas sem intenção ou projectos precisos.
5
6 Projectos explícitos de suicídio (se se proporciona a ocasião). Preparativos de suicídio.

7 – Lentificação. Corresponde a uma dificuldade em iniciar as actividades ou uma lentidão na execução das tarefas quotidianas.

0 Sem dificuldades em iniciar as actividades, sem lentidão.
1
2 Dificuldades em iniciar as actividades
3
4 Dificuldades em iniciar as tarefas quotidianas que são executadas com esforço.
5
6 Grande lassidão. Incapacidade de fazer o que quer que seja sem ajuda.

8 – Dificuldades de concentração.
Corresponde a dificuldades em reunir/ coordenar os pensamentos conduzindo quase à incapacidade de concentração. Cotar em função da intensidade, frequência e grau de incapacidade.

0 Sem dificuldades de concentração.
1
2 Dificuldades ocasionais em reunir/ coordenar os pensamentos.
3
4 Dificuldades em se concentrar e manter a atenção o que reduz a capacidade de ler e manter uma conversação.
5
6 Falta total de concentração. Incapacidade de ler ou de conversar sem grandes dificuldades.

9 – Redução do apetite. Corresponde ao sentimento de uma perda de apetite comparado ao apetite habitual. Cotar a ausência do desejo de se alimentar ou a necessidade de se forçar a comer.

0 Apetite normal ou aumentado.
1
2 Apetite ligeiramente reduzido.
3
4 Sem apetite. Alimenta-se sem gosto pela comida. Necessidade de se forçar a comer.
5
6 Não se alimenta sem ser forçado. Recusa alimentar.

10 – Redução de sono. Corresponde a uma redução da duração ou da profundidade do sono, em comparação com o sono do indivíduo quando não está doente.

0 Sem alterações do sono habitual.
1
2 Ligeiras dificuldades em adormecer ou sono ligeiramente reduzido, ligeiro ou agitado.
3
4 Sono reduzido ou interrompido em menos de duas horas.
5
6 Menos de duas horas de sono

Montgomery SA and Asberg M. A New depression scale designed to be sensitive to change. Brit. J. Psychiatr. 1979;134:382-389.

(Versão Portuguesa - Europeia – Dra. Lara Severino, Profª Dra. Luisa Figueira, Dra. Lara Caeiro).

Asberg M., Montgomery S.A., Perris C., Schalling D., Sedvall G. A comprehensive psychopathological rating scale. Acta Psychiatr. Scand. 1978;271:5-27.

MINI-MENTAL STATE - MMS

NOME: _____
IDADE:_____Anos DATA: _____ de _____ de _____ _____

1. ORIENTAÇÃO (1 ponto por cada resposta correcta).

Em que ano estamos? _____
Em que mês estamos? _____
Em que dia do mês estamos? _____
Em que dia da semana estamos? _____
Em que estação do ano estamos? _____
Em que país estamos? _____
Em que distrito vive? _____
Em que terra vive? _____
Em que casa estamos? _____
Em que andar estamos? _____ Nota:

2. RETENÇÃO (contar 1 ponto por cada palavra correctamente repetida).
"Vou dizer três palavras; queria que as repetisse, mas só depois de eu as dizer todas; procure ficar a sabê-las de cór".
Pèra _____
Gato _____
Bola _____ Nota:

3. ATENÇÃO E CÁLCULO (1 ponto por cada resposta correcta. Se der uma errada mas depois continuar a subtrair bem, consideram-se as seguintes como correctas. Parar ao fim de 5 respostas.)
"Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado volta a tirar 3 e repete assim até eu lhe dizer para parar".
27 __ 24 __ 21 __ 18 __ 15 __ Nota:

4. EVOCAÇÃO (1 ponto por cada resposta correcta.)
"Veja se consegue dizer as três palavras que pedi há pouco para decorar".
Pèra _____
Gato _____
Bola _____ Nota:

5. LINGUAGEM (1 ponto por cada resposta correcta).
a. "Como se chama isto? Mostrar os objectos:
Relógio _____
Lápis _____ Nota:

b. "Repita a frase que eu vou dizer: O RATO ROI A ROLHA" Nota:

c. "Quando eu lhe der esta folha de papel, pegue nela com a mão direita, dobre-a ao meio e ponha sobre a mesa", (ou "sobre a cama", se for o caso); dar a folha segurando com as duas mãos.
Pega com a mão direita _____
Dobra ao meio _____
Coloca onde deve _____ Nota:

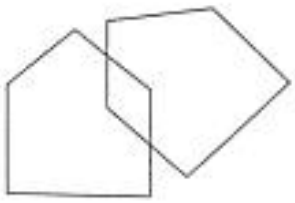
d. "Leia o que está neste cartão e faça o que lá diz". Mostrar um cartão com a frase bem legível, "FECHE OS OLHOS"; sendo analfabeto ler-se a frase.
Fechou os olhos Nota:

e. "Escreva uma frase inteira aqui". Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação.
Nota:

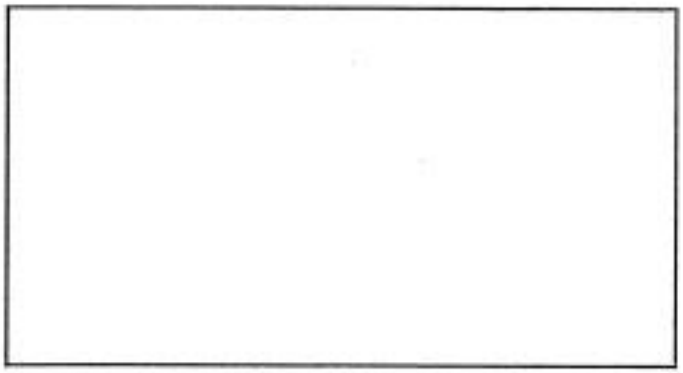
Guerreiro M., Silva A. P., Botelho M. A., Leitão O., Castro-Caldas A., Garcia C., 1994. "Adaptação à População Portuguesa da tradução do "Mini Mental State Examination" (MMSE)". Revista portuguesa de Neurologia; pp: 9-10.

6. **HABILIDADE CONSTRUTIVA** (1 ponto pela cópia correcta.)
Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar, tremor ou rotação.

DESENHO



(Máximo 30 pontos) TOTAL:



FECHE OS OLHOS

Verbal Fluency

Iniciativa Verbal

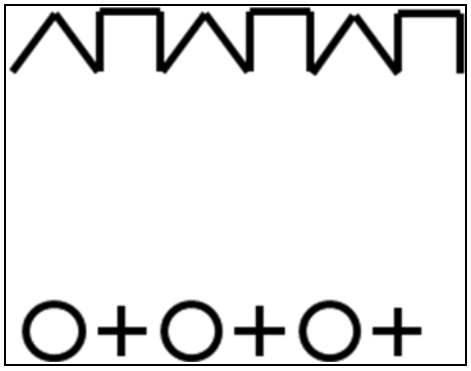
”Gostaria que me dissesse artigos de comer que uma pessoa pode comprar no supermercado (na mercearia). Diga o maior nº de artigos que puder”

_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Total _____/min

Repetitive Sequential Patterns

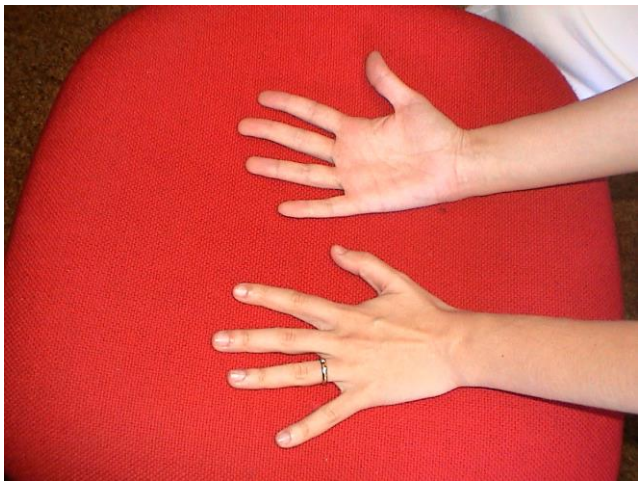
Iniciativa Grafo-motora

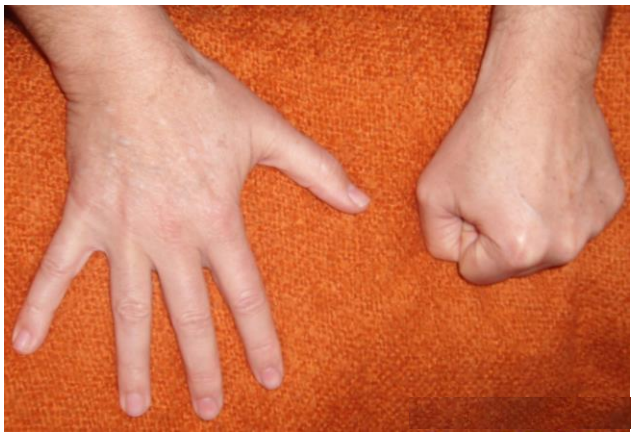


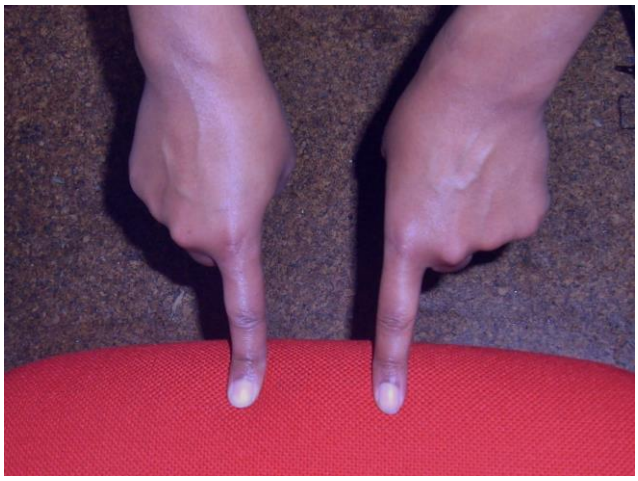
Total _____/2

Repetitive Sequential Patterns

Iniciativa Motora







Total _____/3

Proverbs

Raciocínio Abstracto Verbal

1. “Grão a grão enche a galinha o papo.”

_____

2- “O sol quando nasce é para todos.”

_____

3- “Quem tem telhados de vidro não deve atirar pedras ao do vizinho.”

_____

Classificar cada resposta com:

1 (Literal-pensamento concreto)

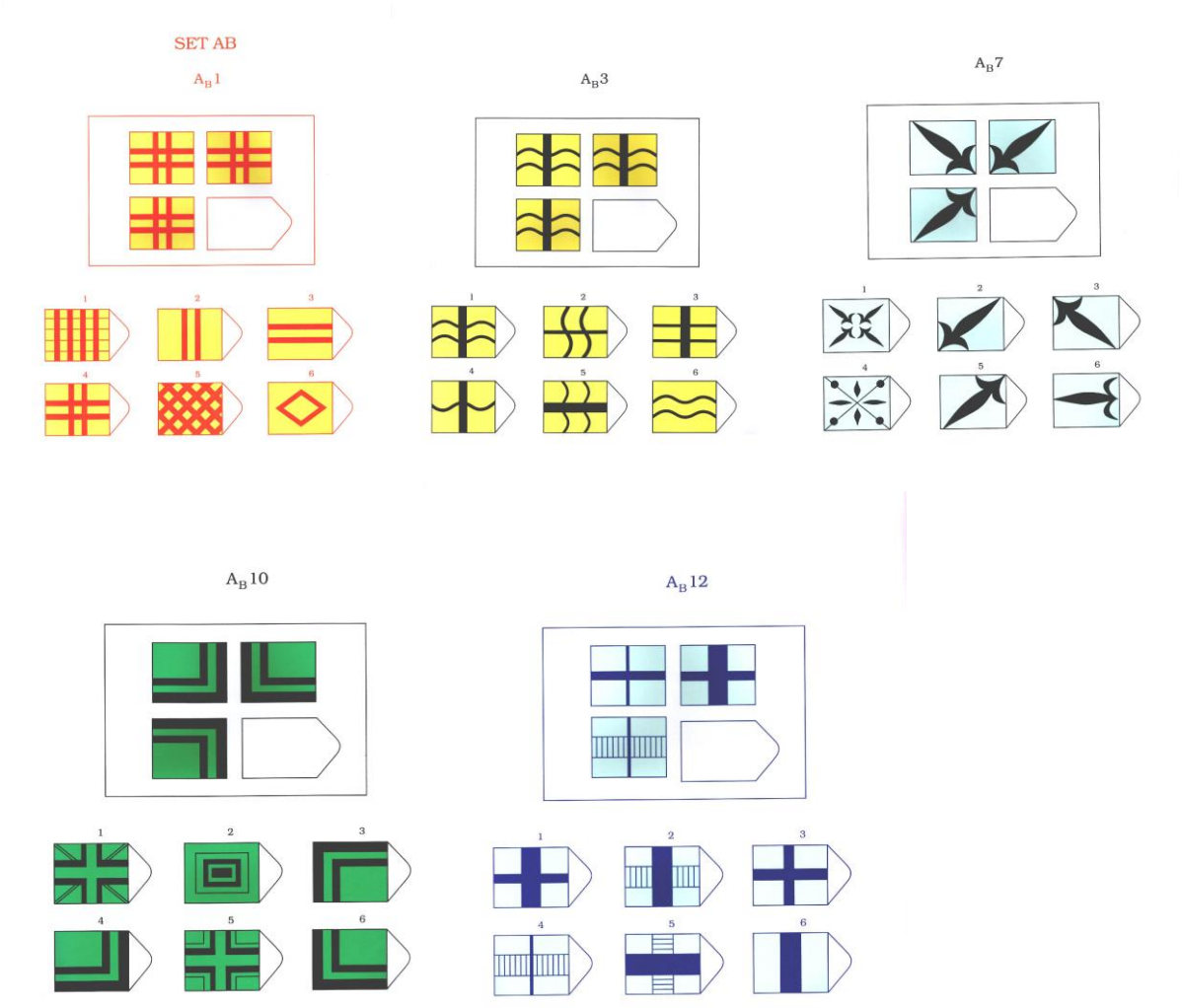
2 (Abstração para apenas uma ideia)

3 (Abstração generalizada, para várias ideias)

Total _____/9

Raven Ab

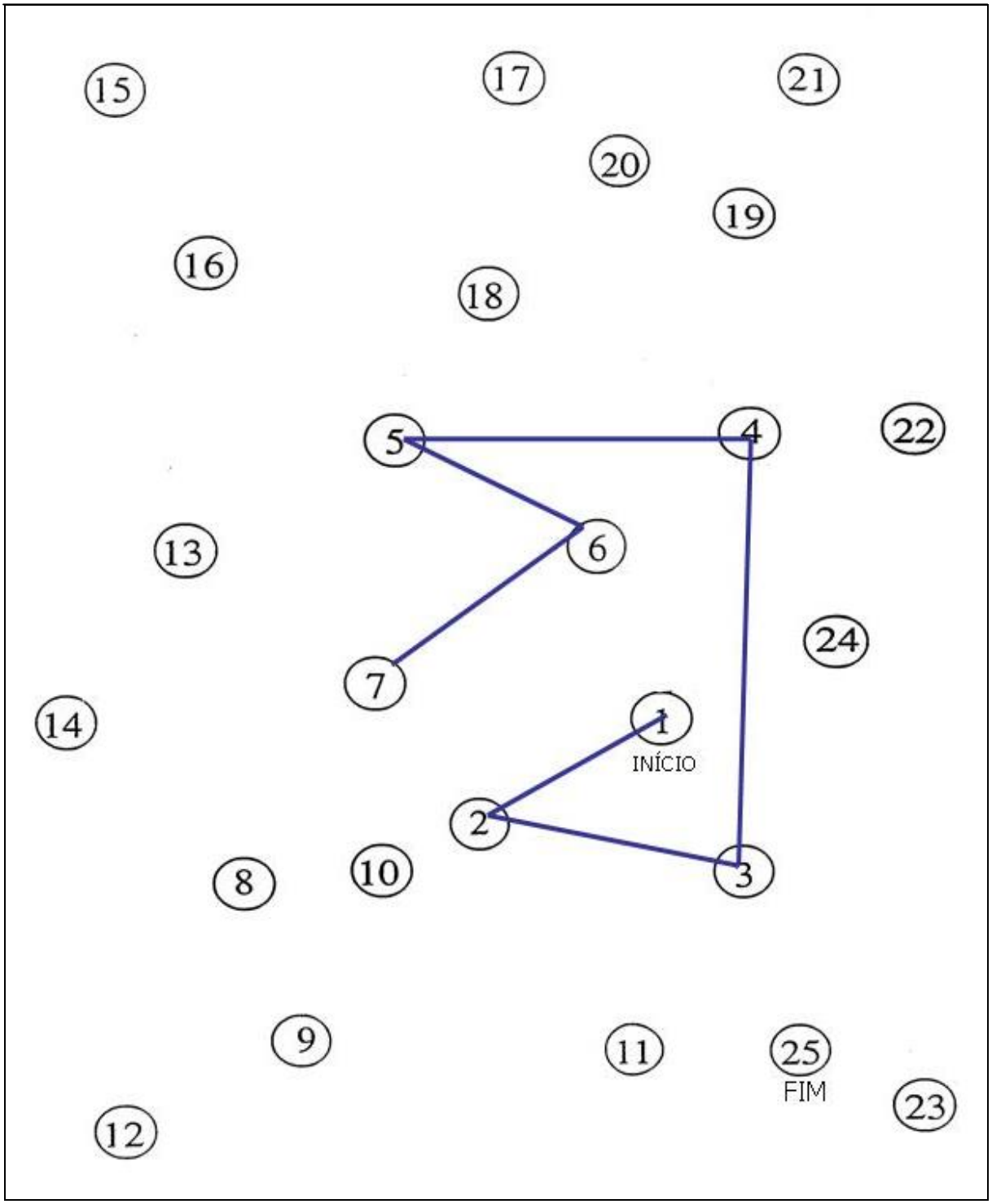
Raciocínio Abstracto Não-Verbal



Total _____/12

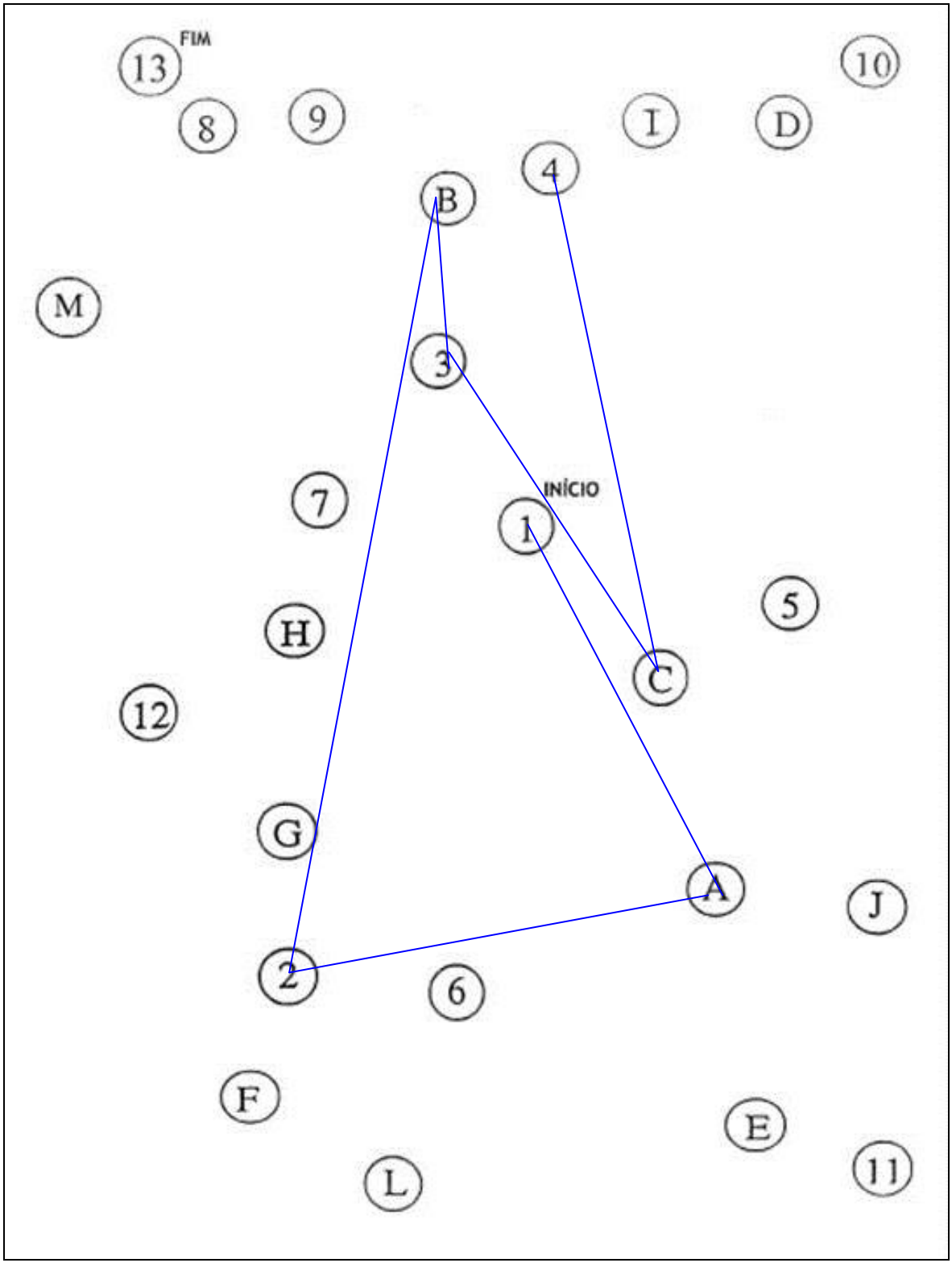
Trail Making Test A

Atenção



Trail Making Test B

Flexibilidade Mental



Barthel Index

Grau Funcional

ÍNDICE DE BARTHEL (na alta ou na 1ª consulta)

ALIMENTAÇÃO: Independente. Capaz de utilizar qualquer utensílio para a acto de comer. Come num período de tempo razoável. Necessita de ajuda, por exemplo, para utilizar o talher. Incapaz
BANHO: Toma-o sem ajuda Dependente
TOILETTE PESSOAL: Lava a a cara, penteia-se, lava os dentes barbeia-se (Consegue manipular a tomada quando utiliza a máquina de barbear) Necessita de ajuda
VESTIR: Independente. Aperta laços dos sapatos, aperta os cintos, abotoa-se. Necessita de auxílio por incapacidade. Totalmente dependente.
CONTROLO INTESTINAL: Sem complicações. Capaz de administrar enema ou supositório se necessário. Complicações ocasionais ou necessita de ajuda quando administra enema ou supositório. Incontinente.
CONTROLO DA BEXIGA Sem complicações. Capaz de recolher a arrastadeira no caso de a utilizar. Complicações ocasionais ou necessita de ajuda com a utilização de arrastadeira. Incontinente.
DESLOCAÇÃO PARA O QUARTO DE BANHO: Independente. Necessita de ajuda para se equilibrar, para o manuseamento de roupas ou de papel higiénico. Dependente.
DESLOCAÇÃO CADEIRA / CAMA: Independente, capaz de manusear o travão da cadeira de rodas e levantar o descanso para os pés. Assistência mínima ou supervisão. Capaz de se sentar embora necessite de total assistência para se deslocar. Incapaz.
DEAMBULAÇÃO Independente durante um percurso de 50 m. Pode utilizar apoios na escada rolante. Precisa de auxílio para percorrer 50 m. Independente, em cadeira de rodas, para um percurso de 50 m, Imóvel.
SUBIR ESCADAS: Independente. Pode utilizar apoios. Necessita de auxílio ou supervisão. Incapaz.
TOTAL

EuroQol

Qualidade de Vida

Mobilidade
Não tenho problemas em andar
Tenho alguns problemas em andar
Tenho de estar na cama

Cuidados pessoais
Não tenho problemas em cuidar de mim
Tenho alguns problemas a lavar-me ou vestir-me
Sou incapaz de me lavar ou vestir sozinho/a

Actividades habituais (trabalho, estudos, actividades domésticas, actividades em família ou de lazer)
Não tenho problemas em desempenhar as minhas actividades habituais
Tenho alguns problemas em desempenhar as minhas actividades habituais
Sou incapaz de desempenhar as minhas actividades habituais

Dor e mal-estar
Não tenho dores ou mal-estar
Tenho dores ou mal-estar moderados
Tenho dores ou mal-estar extremos

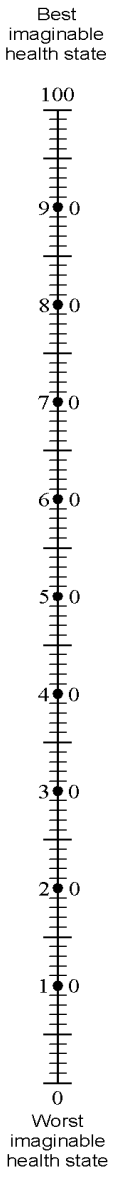
Ansiedade/Depressão
Não estou ansioso/a ou deprimido/a
Estou moderadamente ansioso/a ou deprimido/a
Estou extremamente ansioso/a ou deprimido/a

Adaptado da versão portuguesa do *EuroQol* (EuroQol Group, 2000).
Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 33: 337-343.

EuroQol

Qualidade de Vida

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.



We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Scale Score

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 33: 337-343.

APATHY SECONDARY TO STROKE:

A SYSTEMATIC REVIEW

AND META-ANALYSIS

Lara Caeiro, José M. Ferro, João Costa

Review

Cerebrovascular Diseases

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Apathy Secondary to Stroke: A Systematic Review and Meta-Analysis

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ACKNOWLEDGEMENTS

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We thank the Portuguese Cochrane Collaborating Center for technical support in the conduction of this systematic review.

ABSTRACT

Background: Apathy is a disturbance of motivation, frequent in survivals of stroke. Several studies evaluated the rate of apathy secondary to stroke and risk factors. Different conclusions and contradictory findings have been published. We aimed at performing a systematic review and meta-analysis of all studies evaluating apathy secondary to stroke to better estimate its rate and risk factors, and explore associations with poorer outcomes.

Methods: We searched PubMed, Cochrane Library, PsychINFO and PsycBITE databases and screened references of included studies and review articles for additional citations. Search results and data extraction was performed independently. We systematically reviewed available publications reporting investigations on ischemic and intracerebral hemorrhagic stroke and apathy. Quality assessment of the studies was performed independently. Subgroup analyses were performed according to stroke phase (acute and post-acute), stroke past history (first-ever and any-stroke) and patient age (younger and older patients). Pooled Odds ratios (OR) and Standardized Mean Difference, and 95% confidence intervals (CI), were derived by random-effects meta-analysis. Heterogeneity was assessed with I^2 test.

Results: From the initial 1399 publications, we included 19 studies (2221 patients). Pooled rate of apathy was 36.3% (95%CI 30.3-42.8%; I^2=46.8), similar for acute (39.5% (95%CI 28.9-51.1%) and post-acute phase (34.3% [95%CI 27.8-41.4%]), and about three-times higher than the rate of depression (12.1% [95%CI 8.2-17.3%]). Apathetic patients were older (2.74 years old [95%CI 1.25-4.23]; I^2=0%). No gender differences were found. Depression (OR 2.29 [95%CI 1.41-3.72]; I^2=44%) and cognitive impairment (OR 2.90 [95%CI 1.09-7.72]; I^2=14%) were more frequent, and severe, in apathetic patients. Apathy rate was similar for ischemic and hemorrhagic stroke type and for left and right-sided hemispheric lesions. Clinical global outcome was similar between apathetic and non-apathetic patients.

Conclusion: Apathy secondary to stroke is a more frequent neuropsychiatric disturbance than depression. Apathetic patients are more frequently and severely depressed and cognitively impaired. A negative impact of apathy secondary to stroke on clinical global outcome cannot be ascribed. Future research should properly address its predictor factors and evaluate the impact of apathy treatment options in stroke patients.

1. INTRODUCTION

Apathy is a disturbance of motivation evidenced by diminished goal-directed overt behavior, diminished goal-directed cognition and diminished emotional concomitants of goal-directed behavior [1, 2]. Apathy is thought to be a frequent complication of stroke and a disabling and stressor condition, both for patients and caregivers [3, 4]. Recently, several studies were conducted to specifically evaluate the rate of apathy secondary to stroke, either in the acute or post-acute phases. However, these studies reached different conclusions and contradictory findings have been published [5-7].

Therefore, we aimed at performing a systematic review and meta-analysis of all studies that evaluated apathy secondary to stroke to better estimate its rate and relationship with associated factors, as well as to explore if apathy is associated with a poorer clinical outcome.

2. METHODS

For the purposes of this systematic review we took MOOSE statement as guideline [8].

2.1. Eligibility criteria

Our primary objective was the rate of apathy among stroke patients. Secondary objectives were to explore associations between apathy and age, gender, stroke location (hemispheric left/right) and type (ischemic or intracerebral hemorrhage), depression, cognitive impairment and clinical outcome.

Cases of apathy were all considered for analysis provided that apathy was assessed with validated scales or through clearly defined criteria. Studies that did not specifically mention which validated scales were used for assessing apathy were included, but we performed sensitivity analysis to evaluate the impact of their results in the outcome results. If studies reported only data for cases described as apathy-related disturbances (e.g. abulia, akinesia, mutism, avolition, athymormia, self-activation, indifference), these were only

considered for analysis providing that the definition of these cases clearly referred to diminished motivation, lack of emotion, interest or concern [2, 9, 10].

We considered all types of observational studies or case series. However, the potential risk of bias from selective reporting led us to include only studies in stroke patients that specifically evaluated apathy, either as their primary objective or as a pre-specified outcome. Only ischemic or intracerebral hemorrhagic stroke patients were considered, irrespective of risk factors. Studies enrolling patients with non-vascular cerebral diseases or any type of dementia were excluded. We also excluded case series with less than 10 patients and those including only patients with specific focal stroke locations. This minimum number was chosen to exclude single case reports and small series, therefore decreasing the risk of selection bias.

To decrease detection bias we only included studies based on institutions, either rehabilitation or hospital population. We excluded community-based studies reporting apathy secondary to silent or asymptomatic stroke. We also excluded publications: 1) focusing on the metric properties of scales to assess apathy, with no report on apathy rate secondary to stroke; 2) investigating the relationship between apathy secondary to stroke and silent strokes, white matter lesions or other vascular neuroimaging findings; 3) with stroke patients submitted to brain surgery or endovascular treatment.

2.2. Information sources and search method

Potentially eligible studies were identified through an electronic search of bibliographic databases from inception to April 2012 (Medline through PubMed, Cochrane Library databases, PsychINFO and PsycBITE) and by extensive searching using cross references from original articles and reviews.

The search used the following terms: stroke OR ([ischemia OR infarction OR accident] AND [cerebr* OR brain OR hemisphere OR subcortical OR cortical]) OR cerebrovascular disorders combined with apath* and apathy-related key-words (abulia OR akinesia OR mutism OR avolition OR athymormia OR self-activation OR indifference). All terms were searched as indexed and as free text terms to increase sensitivity. The search was limited to studies conducted on adult humans and published in English, German, French, Spanish or Portuguese. We screened titles, keywords, and abstracts of the citations downloaded from the electronic searches and obtained full copies of potentially suitable

reports for further assessment. For publications with unclear or incomplete data, we contacted the authors asking for further information.

2.3. Study selection and data collection process

Titles and abstracts of obtained records were screened. Doubts and disagreements were solved by consensus. Selected studies were assessed in full-text to determine their appropriateness for inclusion. Two authors independently extracted data from study design, location, time-frame of study, patients' characteristics, studies primary outcome and data of required outcomes.

When two or more publications referring to the same sample were available, we extracted data only from the publication presenting the most accurate estimate, either because of sample size or outcome assessment. For our analysis we used the risk estimate reported in each publication for apathy and associated factors. If no estimate was available, we derived the crude odds ratio from raw data.

Quality assessment of uncontrolled studies is an unsolved issue and debate exists about which should be used in the assessment of risk of bias in case-series studies [11]. We used criteria set derived from those suggested by the Centre Reviews Dissemination York [12, 13] (eAppendix 1 in supplementary material at the end of the manuscript). The quality of reporting was independently analyzed by two authors.

2.4. Statistics and meta-analysis

We used Meta-Analyst [14] and Revman 5.1 [15] software for statistical analysis and to derive forest plots showing the results of individual studies and pooled analysis.

Random-effects meta-analysis weighted by the inverse-variance method was performed to estimate pooled odds ratio (OR) and 95% confidence intervals (95% CI) [16]. Heterogeneity was assessed with the I^2 test that measures the percentage of total variation between studies due to heterogeneity [17]. We used a random-effects model independently of the existence ($I^2 \geq 50\%$) or not of substantial heterogeneity between studies results. The effect measurement estimate chosen was OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects [18]. Raw data was first converted to OR through classic methods or through the

Peto method if one arm had a zero-count cell. When raw data or OR were not available we took the hazard ratio or risk ratio for analysis. When significant associations were found, we determined the differences between apathetic and non-apathetic patients in corresponding rating scores using either the mean difference (MD) or the standardized mean difference (SMD) if studies used the same or different scales, respectively, to assess the outcome.

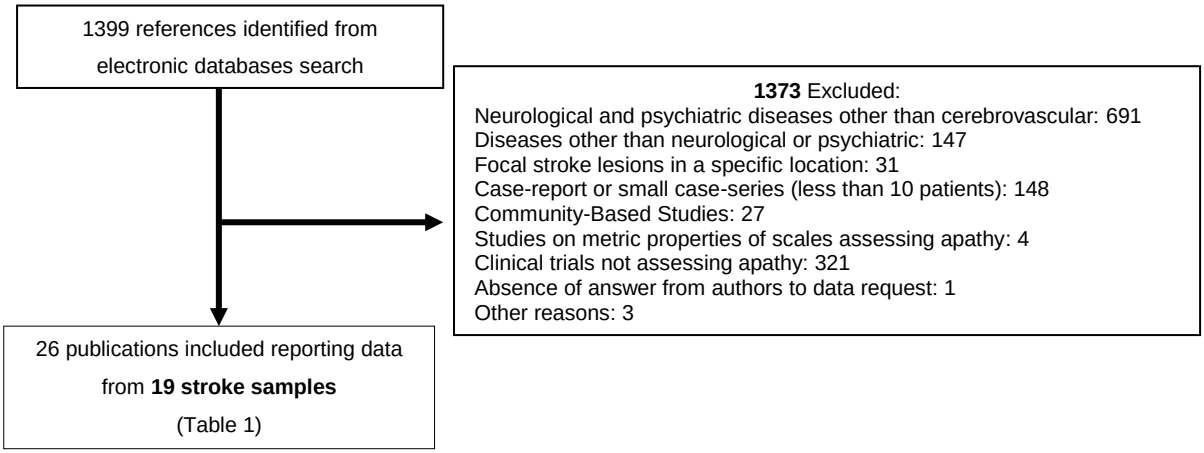
For primary outcome (apathy rate), we presented the results stratified according to stroke phase (acute and post-acute), stroke past history (first-ever and any-stroke) and patient age (younger and older patients) to explore differences in outcome estimates according to these patients subgroups. The cut-off time period used to classify a study as acute or post-acute phase was 15 days from stroke onset. The cut-off used for classifying patients as younger or older was 65 years (mean age). Differences between subgroups were tested using random effects meta-regression. When moderate-to-high heterogeneity (I^2>50%) existed in pooled estimates for the associations between apathy and related factors, we explored if stroke phase, stroke past history or patient age could, at least partly, explain the heterogeneity. A sensitivity analysis excluding studies of poorer quality was conducted to explore the impact of the studies' quality on the results.

3. RESULTS

3.1. Search results

Electronic database search yielded a total of 1399 publications. Following our inclusion and exclusion criteria we were able to include 26 publications reporting data on apathy secondary to stroke. No study reporting data for cases described as apathy-related disturbances met our inclusion criteria. Twelve publications ([19-21], [22, 23], [3, 24], [25, 26], [27-29], [5, 30]) report results for 6 stroke data samples. In these cases, to avoid double counting, we extracted data from the publication presenting the most accurate estimate for the outcome of interest. Therefore, a total of 19 different stroke samples (26 publications) were included for analysis. We excluded one study [31] because no data on the rate of apathy was provided in the publication and the authors did not provide further information after having been contacted. Figure 1 shows the detailed results of the search strategy.

Figure 1. Literature search and results (Systematic review flow-chart).



3.2. Description of studies

Not all studies that evaluated the rate of apathy were prospective. With the exception of two publications, data for our primary outcome could accurately be extracted directly from the publications. In these two cases with unclear data [6, 22, 23], we contacted the authors and further clarification was provided.

A total of 2221 patients were evaluated in these 19 studies (range 29 [32] to 408 [33]). Ten of these studies evaluated more than 100 patients. All included patients with ischemic stroke and 7 studies also evaluated patients with intracerebral hemorrhages, in proportions ranging from 2% to 47.8% [5, 9, 19, 22, 34-36]. Among these 19 studies, 7 evaluated first-ever stroke patients (3 in acute stage and 4 in post-acute stage) [9, 27, 33-35, 37, 38] and 12 included patients independently of prior history of cerebrovascular lesions [3, 5-7, 19, 22, 26, 32, 36, 39, 40, 41]. The timing of apathy assessment after stroke varied across studies from 1-day to 15-months. Seven studies evaluated apathy in the acute stroke phase and 12 in the post-acute phase. Two studies reported the evolution of apathy secondary to stroke over a year [33] or over a 15-months period [3]. With the exception of 3 studies that assessed patients in rehabilitation setting [19, 35, 41], all others were conducted in a hospital setting. Apathy was assessed using one of the following scales: Apathy Scale [42] (n=9), Apathy Evaluation Scale [10, 43] (n=4), Neuropsychiatric Inventory [44] (n=2), Emotion Behavior Index Form [29] (n=1) and Apathy Index Telephone [45] (n=1). In two studies [34, 39], apathy assessment was performed solely based on clinical examination or clinical interview-based questions without using any rating scale. Table 1 shows the main characteristics of included studies.

Table 1. Study characteristics.

Study	n (male %) Mean age (range)	n (%) stroke type Lesion location	Apathy: n (%)	Apathy assessment	Study objectives	Report of significant associations between apathy incidence and clinical factors							
						Exclusion criteria	Stroke type	Stroke location	Age	Gender	Depression	Cognitive impairment	Poor outcome
Acute Stroke (≤15 days) : Hospital setting													
Caeiro L et al [5, 30]	Case-control 94 (64.9%) 55.7 (27-84)	72 (76.6%) infarcts 22 (23.4%) hemorrhages 31 (33%) left; 37 (39.4%) right 69 (73.4%) hemispheric 25 (26.6%) brainstem 20 (21.3%) cortical 26 (27.9%) subcortical	36 (38.3%)	Apathy Evaluation Scale – 10-Item clinical rate	Associations between apathy and stroke, cognitive impairment, depression and functional outcome	TIA, other chronic diseases, deliriums, consciousness disturbances, dementia, aphasia, non-stroke	Intracerebral hemorrhage	Hemisphere Right-sided	No	No	No	No	Yes
Carota A et al [27-29]	First-ever 273 (53%) 64.4 (19-90)	273 (100%) infarcts 122 (53%) left; 107 (47%) right 50 (18.4%) infratentorial 223 (81.7%) supratentorial 58 (21.2%) subcortical 165 (60.4%) Cortical	130 (48%)	Emotion Behavior Index Form	Associations between acute and post-stroke depression (27)	≤1 day hospitalization, delirium, epilepsy, infectious, Parkinson, bilateral or multiple lesions, hemorrhage, severe leukoaraiosis, alcohol abuse, previous non-autonomy	Intracerebral hemorrhage [28]	No	No	No	No	NS	No
Jarzebska E, 2007 [7]	90 (46.6%) 53 (28-72)	90 (100%) infarcts	64 (71%)	Apathy Scale	Frequency of apathy in acute stroke, and the relationship with stroke location and depression	-	NS	Internal carotid artery territory	NS	NS	No	Yes	NS
Kang SY and Kim JS, 2008 [39]	100 (58%) 65.1 (29-88)	100 (100%) infarcts 55 (55%) left; 45 (45%) right	43 (53%)	Clinical observation	Aetiology, clinical and imaging findings in ACA infarction	Non ACA stroke location, SAH, subcortical stroke,	NS	Frontal Left-sided Bilateral	NS	NS	NS	NS	NS
Onoda K et al, 2011 [6]	102 (55.9%) 73.2 (41-96)	102 (100%) infarcts 45 (44.1%) left, 41 (40.2%) right 13 (12.7%) bilateral 42 (41.2%) cortical 76 (74.5%) subcortical	37 (36%)	Apathy Scale	Relationship between post-stroke apathy and regional cerebral blood flow	No lesion (MR), , hemorrhage, dementia, conscious disturbance, aphasia, previous psychiatric illness,	NS	Left-sided basal ganglia	No	No	Yes	Yes	No
Piamarta F et al, 2004 [34]	First-ever 33 (60.6%) 71.6 (60-88)	24 (72.7%) infarcts 9 (27.3%) hemorrhages 19 (57.6%) left; 14 (42.4%) right 5 (15.2%) frontal 16 (48.5%) thalamus/basal ganglia	5 (15.2%)	Clinical interview-based questions	Assess the presence of apathy, anhedonia and emotional lability and depression in first ever supratentorial stroke.	<60 years old, multiple lesion, aphasia, alcohol abuse, previous psychiatric illness.	-	No left -sided No right-sided No subcortical No cortical	No (Correlation)	NS	Yes (Correlation)	No (Correlation)	Yes (Correlation)
Starkstein SE et al, 1993 [9]	First-ever 80 (48.8%) 60 (-)	Infarcts and hemorrhages	18 (22.5%)	Apathy Scale	Frequency and correlates of apathy in stroke	Previous stroke, non-verbal aphasia	No	No	Yes	NS	Yes	Yes	Yes

Table 1. Study characteristics. *(cont.)*

Study	n (male %) Mean age (range)	n (%) stroke type Lesion location	Apathy: n (%)	Apathy assessment	Study objectives	Exclusion criteria	Report of significant associations between apathy incidence and clinical factors						
							Stroke type	Stroke location	Age	Gender	Depression	Cognitive impairment	Poor outcome
Post-acute stage (>15 days): Hospital setting													
Angelelli P et al, 2004 [37]	First-ever 124 (71%) 60.6 (-)	124 (100%) infarcts 53 (42.7%) left; 71 (57.3%) right	33 (26.6%)	Neuropsychiatric Inventory-Apathy	Neuropsychiatric symptomatology and its evolution in stroke	Bilateral lesions, previous stroke, SAH,, chronic diseases, previous psychiatric disease, substance abuse.	NS	NS	NS	NS	NS	NS	NS
Brodaty H et al, [25, 26]	Case-control 135 (60.7%) 72.2 (<85)	135 (100%) infarcts	36 (26.7%)	Apathy Evaluation Scale-Informant	Frequency and clinical correlates of apathy in stroke	>85 years old, hemorrhage, TIA, delirium, non-fluent in English, dementia, alcohol or drug abuse, mental retardation, aphasia.	NS	Right-sided Fronto-subcortical circuit	Yes	No	No	Yes	Yes
Glodzik-Sobanska L, 2005 [38]	Case-control First-ever 31 (51.6%) 62.9 (45–80)	31 (100%) infarcts 16 (51.6%) left; 15 (48.4%) right 31 (100%) hemispheric 4 (12.9%) cortical 18 (50.1%) subcortical 9 (29%) cortico-subcortical	13 (42%)	Apathy Scale	Biochemical changes in frontal lobes and its correlation with apathy	Hemorrhage, multiple stroke lesions, frontal lobe lesion, >80 years old, aphasia, poor clinical status, consciousness disturbances, previous neurodegenerative disease, previous psychiatric disturbances, dementia.	No	No left-sided No right-sided Frontal Lobe	No	No	Yes	NS	NS
Kaji Y et al, 2006 [36]	92 (61%) 64.6 (32-85)	Infarcts and hemorrhages	37 (40.2%)	Apathy Scale	Prevalence and clinical correlates of post-stroke depression including apathy	Conscious disturbances, aphasia, severe cognitive impairment.	NS	No	No	Female	Yes (correlation)	NS	NS
Mayo NE et al, 2009 [33]	First-ever 408 (59.1%) 66.5 (-)	408 (100%) infarcts 177 (43.4%) left; 197 (48.3%) right 18 (4.4%) bilateral	82 (20%)	Apathy Index Telephone (caregivers)	Apathy changes over the 1st year after stroke and its impact on recovery	Severe comorbidity, discharge to long-term care.	NS	NS	Yes	NS	Yes	Yes	Yes
Okada K et al, 1997 [40]	40 (57.5%) 71.4 (-)	40 (100%) subcortical infarcts	20 (50%)	Apathy Scale	Relationship between apathy and regional cerebral blood flow	Aphasia, dementia or Alzheimer	NS	Right dorsolateral frontal and left fronto-temporal	No	No	Yes	Yes	No
Sagen U et al, 2010 [22-23]	104 (59%) 64.5 (-)	99 (95.2%) infarcts 5 (4.8%) hemorrhages	41 (48.8%)	Apathy Evaluation Scale	Identify clinical predictors of anxiety, depression and apathy post stroke	TIA, aphasia,, psychosis, severe cognitive impairment,, terminal illness	NS	NS	Yes	No	No	NS	No
Withall A et al, 2010 [3, 24]	Case-control 106 (48.4%) 74.9 (-)	106 (100%) infarcts	27 (25.5%)	Apathy Evaluation Scale – Informant	Relationship between apathy and depression longitudinally, and its association with dementia	>85 years old, hemorrhage, TIA, consciousness, disturbance, non-English, dementia, alcohol abuse, mental retardation, aphasia	NS	NS	No	No	No	Yes	Yes
Yamagata S et al, 2004 [32]	29 (72.4%) 71.7 (56-87)	29 (100%) subcortical infarcts 11 (37.9%) left; 8 (27.6%) right 10 (34.5%) bilateral	16 (55.2%)	Apathy Scale	Associations between apathy and subcortical cerebral infarctions	Dementia.	NS	Frontal (Fronto-subcortical circuit)	No	No	No	Yes	NS

Table 1. Study characteristics. *(cont.)*

Study	n (male %) Mean age (range)	n (%) stroke type Lesion location	Apathy: n (%)	Apathy assessment	Study objectives	Exclusion criteria	Report of significant associations between apathy incidence and clinical factors						
							Stroke type	Stroke location	Age	Gender	Depression	Cognitive impairment	Poor outcome
Post-acute stage (>15 days): Rehabilitation setting													
Castellanos Pinedo F et al, 2011 [41]	89 (51.7%) - (40-85)	89 (100%) infarcts 45 (50.6%) left; 30 (33.7%) right	31 (34.8%)	Neuropsychiatric Inventory-Apathy	Identify clinical predictors of psychopathological symptoms	Dementia, hemorrhage, other brain injuries, TIA, delirium.	NS	Right-sided	No	No	No	No	Yes
Hama S et al, 2007 [19-21]	243 (66.6%) 65.2 (-)	infarcts or hemorrhages [20] 128 (54%) infarcts 109 (46%) hemorrhages	98 (40.3%)	Apathy Scale	Correlation between stroke basal ganglia lesion or frontal lobe and depression	Previous psychiatric disease, dementia or aphasia, SAH.	No	Bilateral No left-sided No right-sided Basal ganglia	Yes [21]	No [21]	No	No [21]	Yes [21]
Santa N et al, 2008 [35]	First-ever 67 (56.7%) 67.2 (45-90)	35 (52.2%) infarcts 32 (47.8%) hemorrhages 40 (59.7%) left; 54 (80.6%) right	14 (21%)	Apathy Scale	Frequency of apathy after a first-ever stroke and its impact on functional recovery.	Aphasia, dementia.	Infarct	Left-sided basal ganglia No right-sided	Yes	No	NS	Yes	No

NS - “Not Specified” due to missing data in the original or secondary publication

In terms of quality, of the 19 studies, 3 (16%) were rated ‘‘low’’, 11 (58%) ‘‘moderate’’ and 5 (26%) ‘‘high’’. Most studies recruited a representative population (63.2%), used explicit inclusion criteria (84.2%) and consecutively recruited patients (84.2%). However, in only 42.1% and 31.6% of the studies, was it clear that patients entered the study at a similar stage of their disease and were prospectively recruited, respectively. Outcomes assessment was properly made in 89.5% of the studies and almost all studies reported data for prognostic factors (94.7%). The highest risk of study bias was found for follow-up. Only 26.3% of the studies reported and explained loss to follow-up or had a follow-up long enough for important events to occur. Details on quality assessment are provided in supplementary online material (eFigure 1 in supplementary material at the end of the manuscript).

3.3. Outcomes

3.3.1. Rate of apathy

Overall, the frequency of apathetic patients reported in individual studies ranged between 15.2 to 71.1%. Pooled rate was 36.3% (95% CI 30.3 to 42.8%) with moderate heterogeneity (I^2=46.8%). Exclusion of the two studies [34, 39] that did not specify the use of validated scaled for assessing apathy did not significantly changed the pooled result (37.0%; 95% CI 30.5 to 43.9%; I^2=47.0%). Estimates were similar among studies in acute (39.5 % [95% CI 28.9 to 51.1%]; I^2=47.0%) and post-acute (34.3 % [95% CI 27.8 to 41.4%]; I^2=45.7%) stroke phases (subgroup difference: 4.7%; 95% CI -7.6 to 17.1%; p=0.455; Figure 2A). Apathy rate was significantly lower (-14.3%; 95% CI -2.2 to -26.5%; p=0.021; Figure 2B) among first-ever stroke (27.1%; 95% CI 18.0 to 38.7%; I^2=47.7%) than any-stroke (41.6%; 95% CI 35.0 to 48.6% I^2=44.9%) studies. The difference in apathy rate (9.4%; 95% CI -2.4 to 21.3%; p=0.118; Figure 2C) between studies evaluating younger (41.7%; 95% CI 32.1 to 52.0%; I^2=46.7%) and older patients (32.4%; 95% CI 25.8 to 39.8%; I^2=45.7%) was not significant. Meta-regression also failed to show a significant relationship between apathy rate and patients mean age (95% CI for regression coefficient: -0.046 to 0.006; p=0.140; eFigure 2).

The rate of apathy without concomitant depression was reported in 9 studies with a pooled estimate of 21.4% (95%CI 15.6 to 28.7%; I^2=45.6%). This rate was also lower in first-ever studies (-15.6%; 95%CI -4.9 to -26.3%; p=0.004) and similar between acute *vs*. post-acute and between younger *vs*. older patients (p>0.83 for both comparisons). Figures 2D, E and F show the main results for apathy rate without concomitant depression.

Figure 2. Rates of apathy

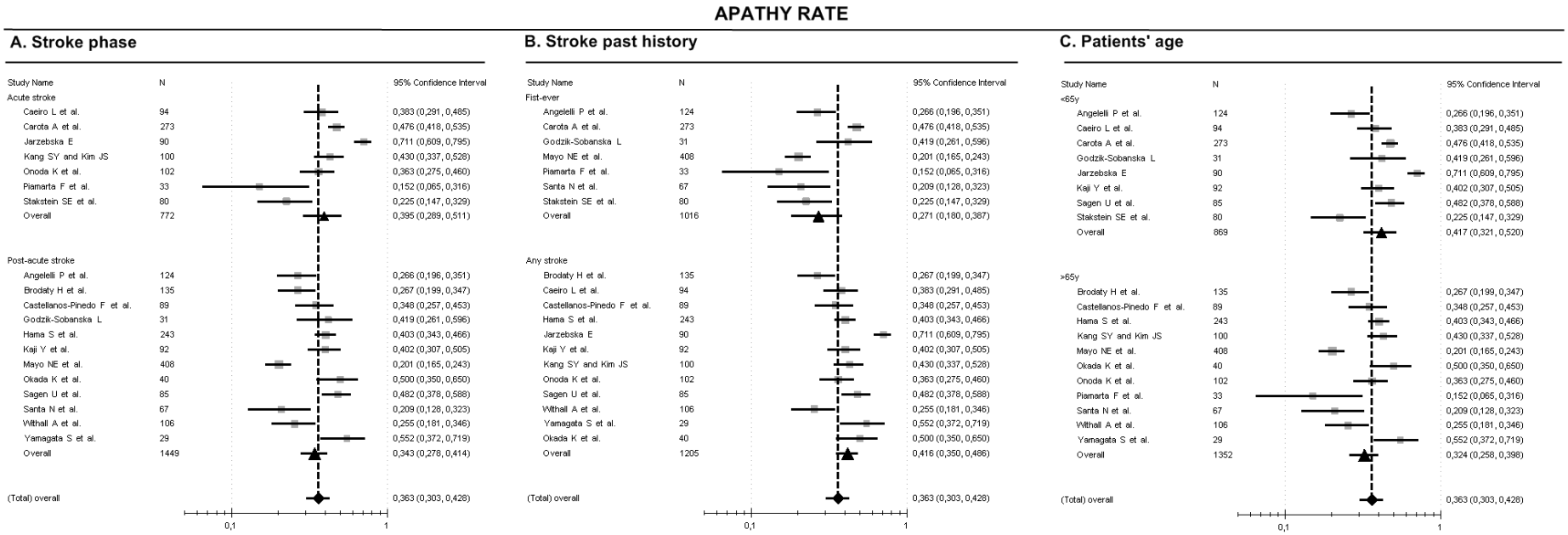
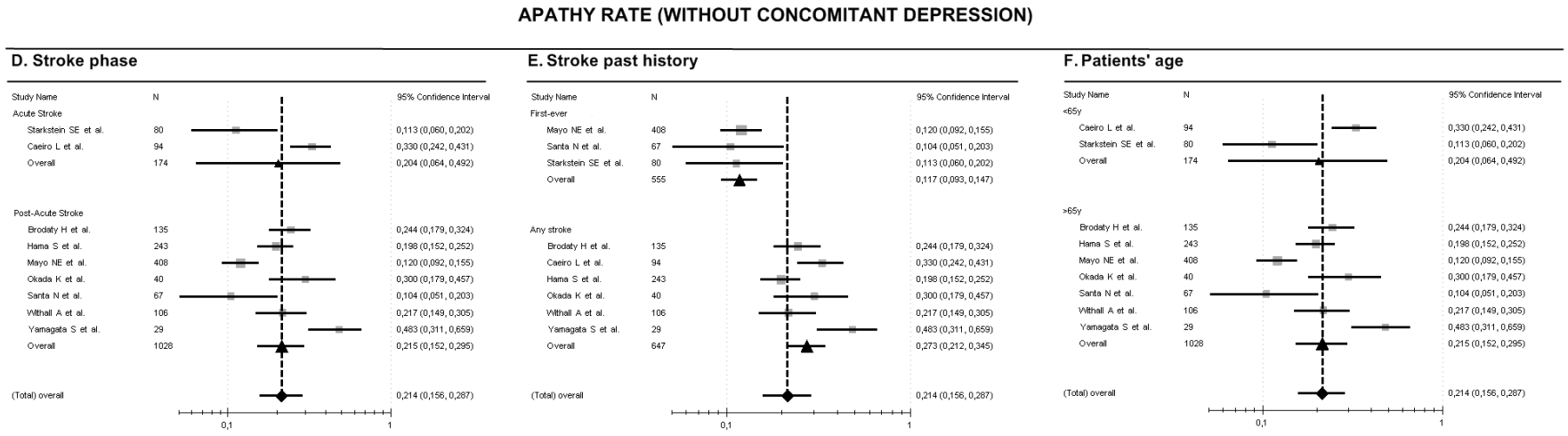


Figure 2. Apathy Rate (without concomitant depression)



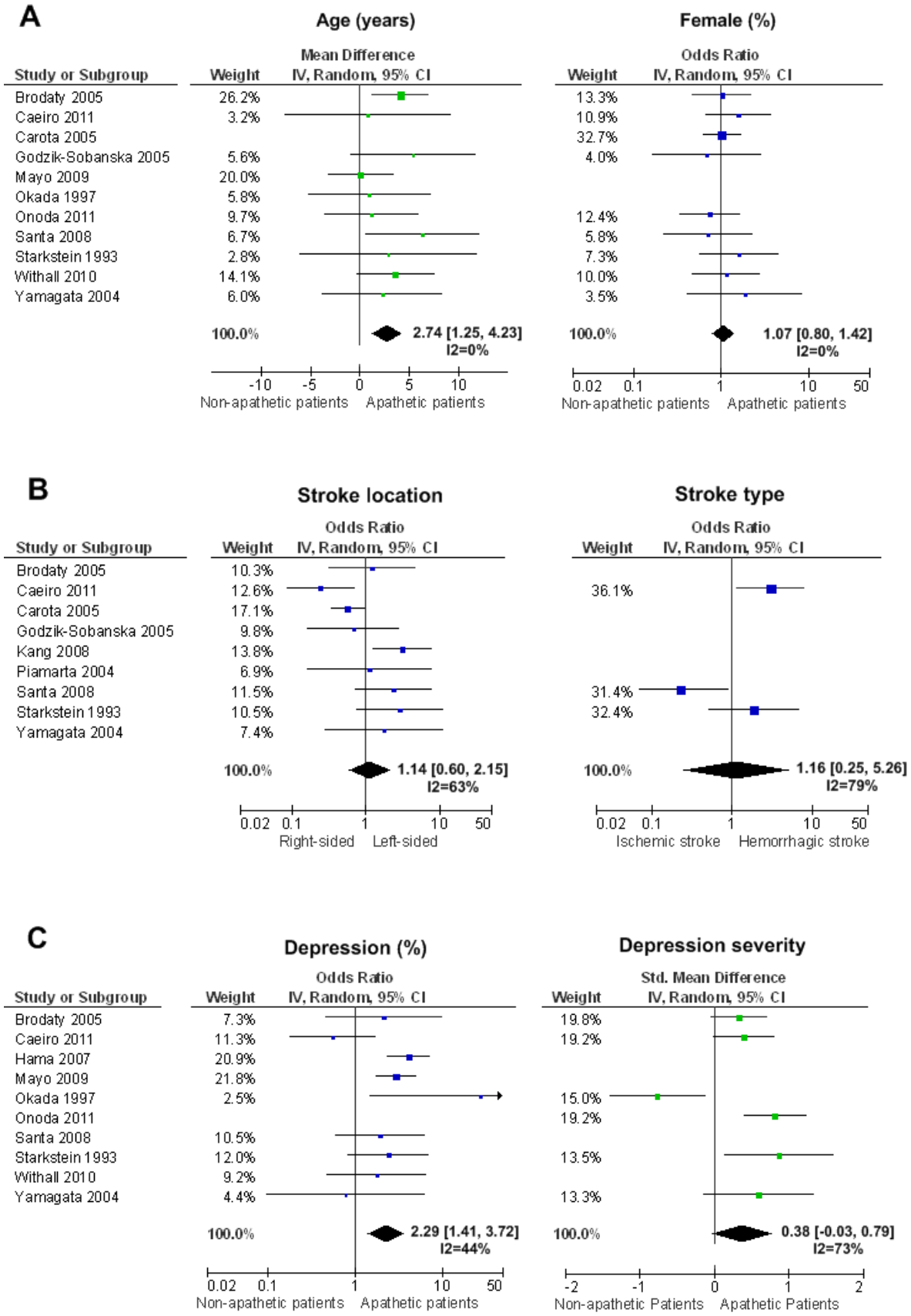
Two studies provided longitudinal data for apathy rate. In one study [3], about 55% of the patients who were apathetic at 4 months remained apathetic (with or without concomitant depression) at 15-months. In this study, dementia was found to be a risk factor for apathy. In the other longitudinal study [33], serial measures of apathy over time (12 months) were taken to estimate the extent of each apathy change. According to the authors, the majority (50%) of the patients demonstrated apathetic behavior rarely and was classified as “low-apathy”. In about one-third of the patients, the extent of apathetic behavior remained stable, while in the others, apathy either increased (7%) or improved (7%) over time. Older age, cognitive impairment and functional disability were found to be predictors of apathy after stroke. In this study, “high-apathy” had a significant negative effect on clinical outcomes.

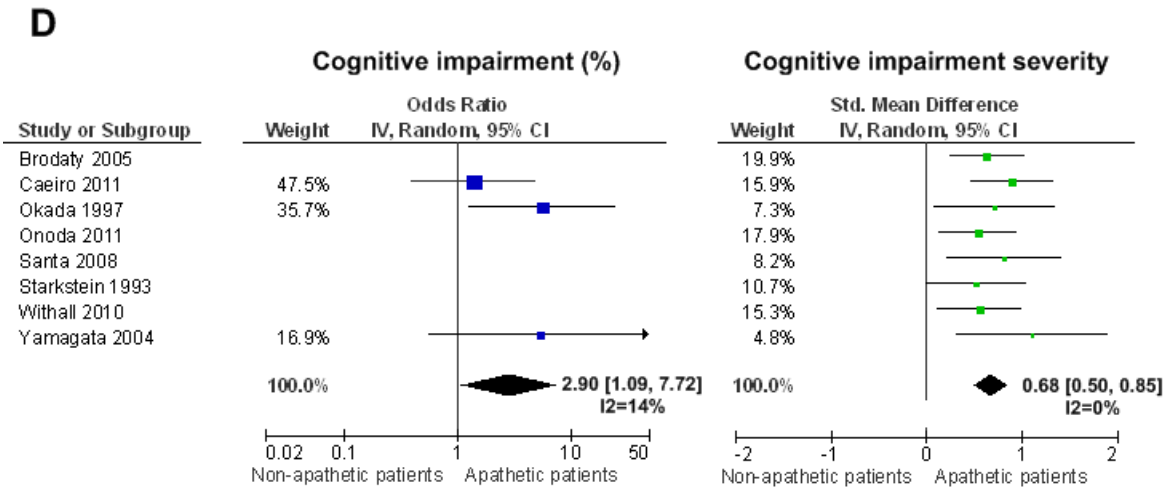
3.3.2. Apathy and associated factors

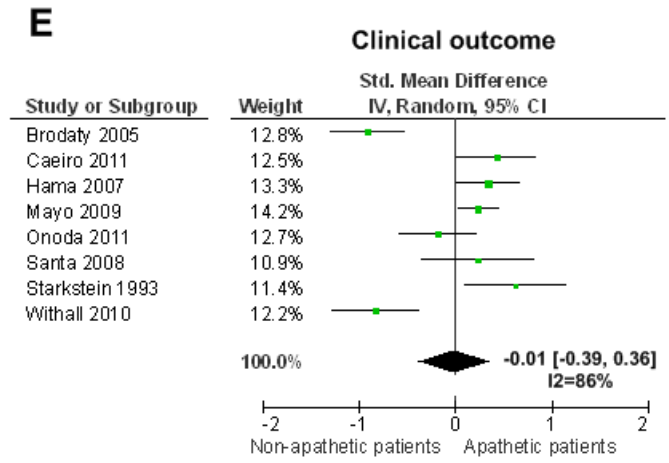
Overall, apathetic patients were about 3 years older than non-apathetic patients (2.74 years old [95% CI 1.25 to 4.23]; I^2=0%). The proportion of females (OR 1.07 [95% CI 0.80-1.42]; I^2=0%) and males (OR 0.88 [95% CI 0.66-1.17]; I^2=0%) was similar among apathetic and non-apathetic patients (Figure 3A).

Rate of apathy was similar in patients with left and right-sided hemispheric lesions (OR 1.14 [95% CI 0.60-2.15]; Figure 3B). However, significant heterogeneity existed between the studies’ results (I^2=63%). Although similar results were found for acute and post-acute stroke phase studies, no heterogeneity existed for post-acute stroke results. On the other hand, pooled results for studies evaluating older patients showed a significantly higher rate of apathy in left-sided lesions, without heterogeneity (OR 2.13 [95% CI 1.19 to 3.80]; I^2=0%). Results were similar for first-ever and any-stroke, and both had significant heterogeneity (eFigure 3A).

Figure 3. Apathy and associated factors







Only three studies provided data for the analysis of the association between the rate of apathy and stroke type, which precludes strong conclusions. Overall, rate of apathy was similar between patients with hemorrhagic and ischemic strokes (OR 1.16 [95% CI 0.25-5.26]; Figure 3B). The high heterogeneity (I^2=79%) could at least partly be explained by the stroke phase and patient age. Two out of the three studies that provided data for this outcome evaluated younger patients in an acute stroke phase. In pooled results from these two studies, apathy was more frequent after hemorrhagic than ischemic stroke (OR 2.58 [95% CI: 1.18 to 5.65]; I^2=0%; eFigure 3B), while in older post-acute stroke patients apathy was less frequent after hemorrhagic stroke (OR 0.23 [95% CI 0.06 to 0.90]). Past history of stroke did not explain heterogeneity and no significant differences existed between first-ever and any-stroke studies.

The overall rate of depression without concomitant apathy found in included studies was 12.1% (95% CI 8.2-17.3%; I^2=43.4%). Depression was more common in apathetic than in non-apathetic patients (OR 2.29 [95% CI 1.41-3.72]; I^2=44%; Figure 3C). Depression severity, as assessed through validated scales (Montgomery and Asberg Depression Rating Scale, Hamilton Depression Rating Scale and Self-rating Depression Scale), was higher in apathetic patients (SMD 0.38 [95% CI -0.03-0.79]; I^2=73%), although it did not reach significance (p=0.07; Figure 3C). The high heterogeneity (I^2=73%) could at least partly be explained by the stroke phase and patient age. Pooled results from the three acute-phase studies (SMD 0.65 [95% CI 0.35 to 0.95]) and the two studies evaluating younger patients (SMD 0.53 [95% CI 0.12 to 0.94]) showed a significantly higher depression severity with low heterogeneity (I^2=13%; eFigure 3C).

The overall rate of patients with cognitive impairment found in included studies was 20.2% (95% CI 10.1-36.5%; I^2=42.5%). Cognitive impairment was more common in apathetic than in non-apathetic patients (OR 2.90 [95% CI 1.09-7.72]; I^2=14%), although this estimate is based on data from only 3 studies (Figure 3D). Severity of cognitive impairment, as assessed through Mini-Mental State Examination and Hasegawa Dementia Rating Scale Revised, was higher in apathetic patients (SMD=0.68 [95% CI 0.50-0.85]; I^2=0%; Figure 3D).

Severity of clinical global outcome, as assessed through validated scales (Modified Ranking Scale, Johns Hopkins Functioning Inventory, Instrumental Activities of Daily Living, Functional Independence Measurement and Barthel Index), was not significantly different between apathetic and non-apathetic patients (SMD -0.01 [95% CI -0.39-0.36]), although significant heterogeneity (I^2=86%) exists among studies (Figure 3E). The high heterogeneity could at least partly be explained by the stroke past history and patient age. Pooled results from the three first-ever stroke studies (SMD 0.29 [95% CI 0.10 to 0.48]) and the two studies evaluating younger patients (SMD 0.53 [95% CI 0.12 to 0.94]) showed a significant poorer clinical outcome in these apathetic patients with low heterogeneity (I^2=0 to 13%; eFigure 3D).

In general, the results for the different outcomes did not change after excluding the studies rated as “low-quality” from the analysis including the two studies [34, 39] that evaluated apathy through clinical observation without specifying the use of validated scales (sensitivity analysis). The only two exceptions were depression severity which became significantly worse in apathetic patients (SMD 0.55 [95% CI 0.28-0.81]) and the rate of cognitive impairment which became non-significant (OR 1.4 [95% CI 0.39-4.96]).

4. DISCUSSION

Apathy is thought to be a frequent complication of stroke associated with poorer outcomes, but available clinical data lacks strength and published results have been contradictory. We performed a systematic review and meta-analysis of all studies evaluating apathy secondary to stroke to better estimate its rate and risk factors, and explore associations with poorer outcomes. The most relevant findings of our study are: (1) Apathy secondary to stroke is a frequent neuropsychiatric disturbance affecting 1 in every 3 stroke patients; Apathy rate is lower in patients without previous cerebrovascular disease; Rate of "pure" apathy (without concomitant depression) is twice as frequent as the rate of "pure" depression (without concomitant apathy); (2) Apathetic patients are about 3 years older than non-apathetic patients without gender differences; (3) Rate of apathy was similar for left- and right-sided hemispheric stroke lesions and for ischemic and hemorrhagic stroke type; (4) Apathetic patients are more frequently and severely depressed and cognitively impaired in comparison to non-apathetic patients; (5) Overall, apathy secondary to stroke does not appear to have a negative impact on clinical global outcome, except for apathetic patients with first-ever stroke and for younger patients.

Our conclusions are based on 19 studies that evaluated apathy secondary to stroke (7 in acute phase and 12 in post-acute phase) enrolling a total of 2221 patients. The overall quality of the studies was considered to be moderate. The highest risk of bias was found for follow-up (duration, reporting and explanation of lost cases). In most of the studies it is unclear if patients were prospectively recruited. These aspects increase the risks of detection and selective reporting. However, sensitivity analysis by excluding studies rated "low-quality" did not significantly change the overall results.

We found high statistical heterogeneity ($I^2 \geq 50\%$) among the studies' results for stroke lesion lateralization and type and for depression and clinical global outcome severity, but not for the other outcomes. The heterogeneity found in these outcomes was most probably due to differences in stroke phase (acute and post-acute phase) and history (first-ever and any-stroke), patient age (younger and older) and study quality. In fact, heterogeneity decreases when considering the results for each stroke subgroup separately and after excluding the studies rated as low-quality from the analysis.

We were conservative in our analysis because we did not consider undefined data, and when studies presented different estimates we extracted those reporting only the most precise or adjusted measure. We were also able to retrieve unpublished information from

two studies. Nevertheless, moderate heterogeneity exists among studies in our primary outcome.

The rates of apathy secondary to stroke found in our study are undoubtedly large, which could be due to the absence of a clear nosological definition or clinical criteria [46, 47]. However, the mean ages of included samples (range, 53 to 75 years old) were lower than that usually reported in hospital-based stroke samples, which could indicate the presence of selection bias in the included studies and result in an underestimate of apathy rate. In the two studies that provided longitudinal data [3, 33], about half of the apathetic patients remained apathetic long after stroke onset and most of these cases rarely had apathetic behaviors. Older age, cognitive impairment and functional disability were found to be predictors of apathy after stroke.

According to our results, apathetic patients were older and more frequently and severely cognitively impaired. These results are in agreement with recent prospective healthy community-dwelling populations' studies [48, 49]. Similar to the results from longitudinal post-stroke studies [3, 33], in these studies the frequency of apathy increased with age and was positively correlated with the presence and severity of cognitive impairment. Furthermore, apathy was associated with cognitive and functional impairments in elders adjudged to have normal cognition [48]. It has been reported that up to a quarter of non-demented community-dwelling elderly individuals have apathy (most without concomitant depression) [50, 51]. In this population a past history of stroke (OR 1.8; 95% CI: 1.4 to 2.3) [50] or other vascular diseases are risk factors for apathy [51]. The prevalence of apathy is significantly higher in demented patients [52]. A prospective multicenter study evaluating 684 community-dwelling elderly patients with Alzheimer disease reported an apathy point prevalence of 43%, which was associated with functional disability [53]. Other studies in community-dwelling elderly patients with dementia have reported even higher apathy prevalence rates [54]. Similar to non-demented older people, a previous history of stroke also increases the risk of apathy (OR 4.5; 95% CI: 1.3 to 15.6) in older demented people [55]. In summary, apathy is a common condition in older persons and in particular in older cognitively impaired people. Stroke is a risk factor for apathy in both.

In a review with five studies, Jorge et al. [56] drew attention to the fact that apathy is often associated with depression, but one can occur separately from the other. We found that the rate of apathy without depression was twice that of depression without apathy, further reinforcing the notion that these are different clinical entities. On the other hand, our results also show an association between apathy and depression, as apathetic patients are more frequently depressed and apathy rate increases 15% in the presence of depression. In

a prospective study that specifically evaluated the relationship between apathy and depression following stroke, no significant overlap between both syndromes were found at index assessment [3]. However, apathy and depression overlap longitudinally one year after stroke possibly indicating that cumulative vascular lesions are an important risk factor for both. Furthermore, dementia was a common risk factor for both syndromes in stroke patients.

Apathy and depression share symptoms such as diminishing interest in daily activities and decrease in motion activity. Patients with both neuropsychiatric disturbances after stroke share common neuropsychological features such as low MMSE scores [3] and working memory impairment [26]. Specific subcortical stroke locations can induce both apathy and depression [3, 26].

We found no differences in the rate of apathy according to the hemispheric stroke side location, except for older ages, which have apathy more frequently after left-sided stroke lesions. Jorge et al. [56] suggested that stroke involving subcortical areas of the cortico-subcortical circuits is associated with apathy. Specific stroke locations have been reported to be related to apathy namely basal ganglia lesions (leading to a dysfunction of the fronto-subcortical system) [6] with possible involvement of the dopaminergic and glutamatergic systems [38, 57], anterior thalamic acute lesions [58, 59], polar-paramedian thalamic lesions [57] and amygdala lesions [25]. Abulia in post-acute stroke phase was found in 55% patients with caudate stroke lesions [60]. However, these statements are based on reports investigating apathy in patients with specific focal stroke location without controls. We have not included these studies in our analysis to decrease selection bias.

Although some publications suggested the existence of an association between apathy secondary to stroke and a lower functional status [56], our results do not confirm those claims, except for samples including first-ever stroke and younger patients. The apparent discrepancy of our finding may be related to characteristics of apathy itself because apathetic patients may be less aware or report fewer complains about a loss of functionality.

Our systematic review has several limitations. The results and conclusion are weakened by limitations inherent to meta-analysis and individual studies. Except for the rate of apathy (our primary outcome), a significant number of publications did not report data for other outcomes, in particular for the relationship between apathy and associated factors. Our analysis included only institution-based studies. Although our results are in close agreement with those from prospective community-dwelling populations' studies, they

should be generalized with caution to the overall post-stroke population. Furthermore, studies also used different scales to evaluate apathy, depression, cognitive impairment and clinical global outcome. None of the studies reported information about stroke severity, which may have had a negative impact on motivational status. The overall quality of included studies was moderate. However, reporting quality for a few studies was low and selective and detection bias cannot be ruled out. The exclusion of publications written in languages than English, Spanish or French, as well as of non-published studies, may increase the risk of publication bias. Nevertheless, we were able to obtain non-published data from two studies and visual inspection of funnel plots shows symmetry, suggesting that publication bias was not a major drawback of our review.

In conclusion, in hospital and rehabilitation-based studies apathy secondary to stroke is a common neuropsychiatric disturbance both in acute and post-acute phases. Future research is needed to properly address how apathy and depression are related and affect cognitive functioning, specifically executive functioning. Representative prospective cohort-studies with Diffusion-Weighted MR Imaging that properly evaluate longitudinally apathy and its association with stroke type and severity, as well as with concomitant outcomes, are strongly needed. The high rate of post-stroke apathy should also prompt the evaluation of therapeutic options for apathy treatment.

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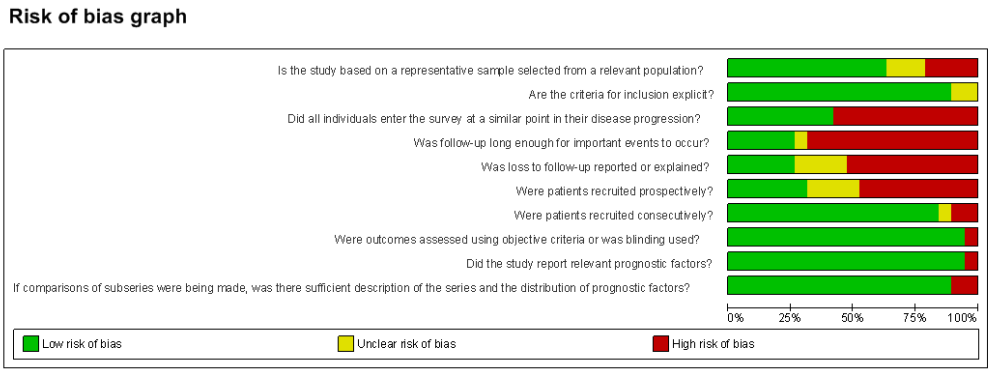
eAppendix 1. Criteria used for quality assessment (derived from CRD).

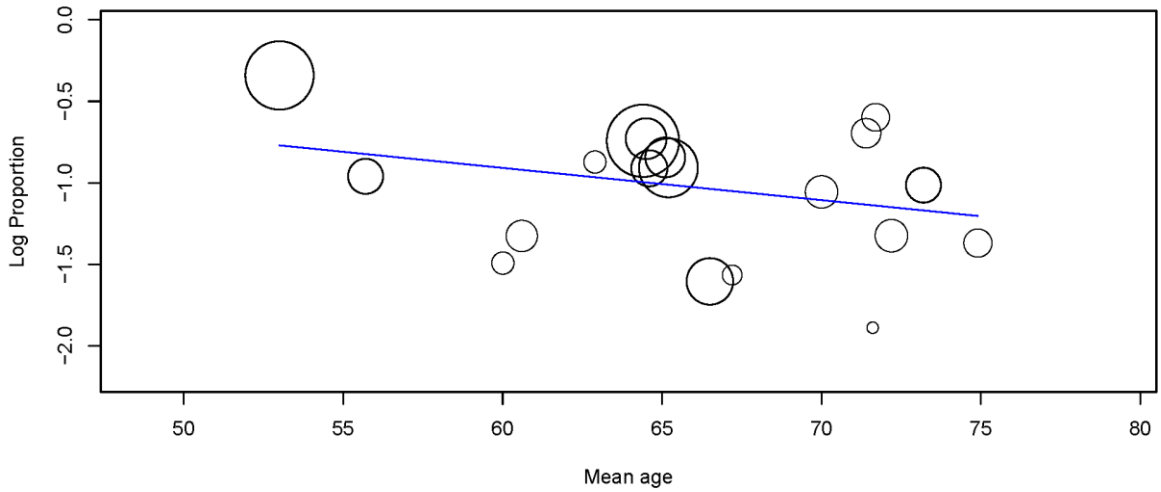
1. Is the study based on a representative sample selected from a relevant population?
2. Are the criteria for inclusion explicit?
3. Did all individuals enter the survey at a similar point in their disease progression?
4. Was follow-up long enough for important events to occur?
5. Was loss to follow-up reported or explained?
6. Were patients recruited prospectively?
7. Were patients recruited consecutively?
8. Were outcomes assessed using objective criteria or was blinding used?
9. Did the study report relevant prognostic factors?
10. If comparisons of subseries were being made, was there sufficient description of the series and the distribution of prognostic factors?

Case series quality rating = “High-quality” if the study scored 8 to 10; “Moderate quality” if the study scored 5 to 7; and “Low-quality” if the study scored 0 to 4.

eFigure 1. Risk of Bias

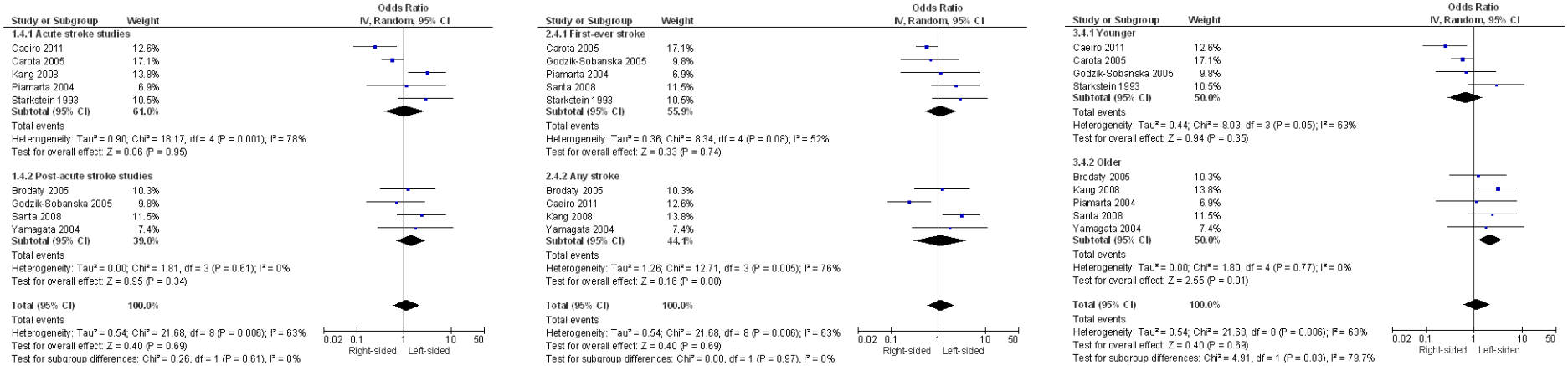


eFigure 2.



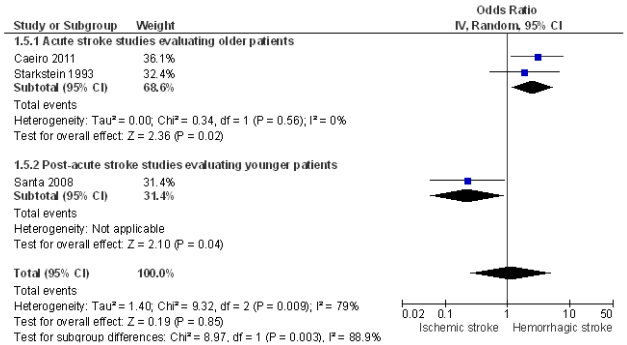
eFigure 3A. Apathy and Stroke Location

eFigure 3A. Apathy and stroke location

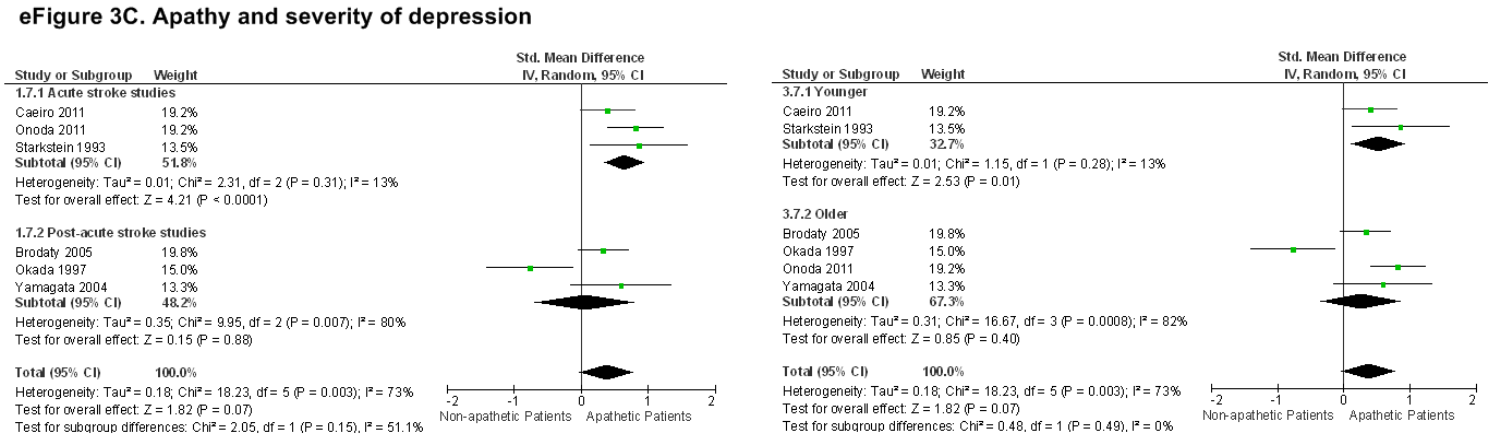


eFigure 3B. Apathy and Stroke Location and Stroke Type

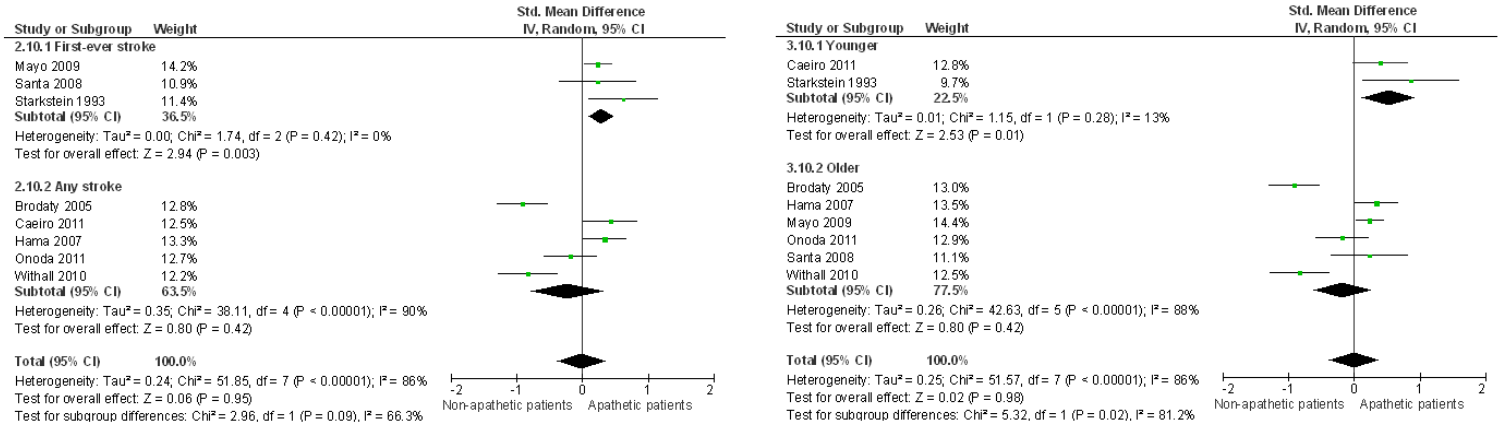
eFigure 3B. Apathy and stroke type



eFigure 3C. Apathy and Severity of Depression



eFigure 3D. Apathy and Severity of Depression and Clinical Global Outcome



Metric Properties of the Portuguese Version of the Apathy Evaluation Scale

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METRIC PROPERTIES OF THE PORTUGUESE VERSION OF THE APATHY EVALUATION SCALE

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“O estudo dos instintos, das paixões... só é possível pela abordagem exterior, por meio dos factos materiais que os traduzem, não há acesso direto à consciência que lhes dá origem.”

“O método experimental permite estudar as variações do fenómeno da consciência, não a própria consciência.”

In Junior WAF

[*Nietzsche e Théodule Ribot: Psicologia e superação da metafísica.* Nat Hum (Online)]

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The authors would like to express their gratitude to Vera Caeiro and Marco Machado who translated the Apathy Evaluation Scale English version into Portuguese and retroversion of the Portuguese version into English.

ABSTRACT

The clinical-rated and self-rated versions of the Apathy Evaluation Scale are validated for English language. The Apathy Evaluation Scale is useful to characterize and quantify apathy. We analyzed the metric properties of the Portuguese version of the Apathy Evaluation Scale-Clinical and of a new 10-item short version of the clinical-rated and self-rated versions Apathy Evaluation Scale. We included, 156 “healthy participants”, 40 healthy “elderly participants”, 21 patients with dementia, and 21 patients with depression, comprising a sample of 238 individuals. We studied reliability using Cronbach Alpha (α) and Split-half method, and construct validity using principal component analysis with Varimax rotation. The clinical-rated and self-rated Portuguese versions of the AES are valid instruments to measure apathy in Portuguese speaking individuals. Both the clinical-rated and the self-rated versions Apathy Evaluation Scale can be used instead of the long versions of the Apathy Evaluation Scale.

RESUMO

As versões clínica e de auto-avaliação da Escala de Avaliação da Apatia estão validadas na versão original inglesa. A Escala de Avaliação da Apatia é utilizada para caracterizar e quantificar a apatia. Nós analisámos as propriedades métricas das versões portuguesas da Escala de Avaliação da Apatia, e também de uma versão reduzida da escalas clínica e de auto-avaliação, mas com apenas 10-items. Incluímos 156 “participantes saudáveis”, 40 “participantes idosos saudáveis”, 21 pacientes com demência, e 21 pacientes com depressão, fazendo uma amostra total de 238 indivíduos. Estudámos o nível de fidelidade suportado pelo Alpha (α) de Cronbach e com o método *Split-half,* e a validade de construto através da análise dos componentes principais com rotação de Varimax. Na sua versão Portuguesa, tanto a Escala de Avaliação da Apatia clínica como a de auto-avaliação são instrumentos válidos para medir a apatia em sujeitos portugueses. As versões clínica e de auto-avaliação reduzidas de 10-items podem ser utilizadas em substituição das versões mais longas da Escala de Avaliação da Apatia.

1. INTRODUCTION

Apathy is a lack of motivation with simultaneous decrease in behavioural, cognitive and emotional concomitants of goal-direct behaviour (Marin, 1991; Marin, Biedrzycki & Firinciogullari, 1991) which could lead to an "indifference and lack of response to one's surroundings" (American Psychological Association, 2007, pp. 65). Apathy is a neurobehavioral syndrome and may comprise aboulia (an extreme loss of will, but expressed by an absence/reduction of spontaneous acting, and thinking), avolition (failure to engage in goal direct-behaviour), athymormia (loss of motor and/or affective auto-activation but not of heteroactivation), and/or affective indifference to any stimulus (American Psychiatric Association (APA), 2002; Marin et al., 1991; Marin, 1990; Sadock & Sadock, 2003). Thus, for the evaluation of apathy it is important to ask for motivation but also observe behaviour, cognition and emotional responses (Marin et al. 1991).

Apathy secondary to a medical condition such as in schizophrenia, depression, Alzheimer's dementia, vascular dementia or fronto-temporal dementia, Parkinson's disease, and stroke, was defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2002) as a personality disturbance. Apathy interferes with a patient's ability to fulfil daily and social activities (Iancu, Tschernihovsky, Bodner, Piconne, & Lowengrub, 2010). If patients start rehabilitation programs the Apathy Evaluation Scale (AES) may be used for monitorization (Resnick, Zimmerman & Adelman, 1998).

The original English version of the AES was developed and validated by Marin et al. (1991). The original AES aimed at characterizing and quantify apathy in patients older than 55 years old, with the AES clinical-rate (AES-C), AES self-rated (AES-S) and AES informant rate, in a healthy sample and in samples of patients with depression or dementia. For the principal components factor analysis Marin et al. (1991) identified three factors. Internal consistency was high for the clinical rate (coefficient α=.90) and for the self-rated version (coefficient α=.86) (Marin et al. 1991). The two versions were highly correlated (r=.72, p=<.01). Following the Marin et al. (1991) publication, data from 31 healthy controls revealed that participants would be apathetic if scoring a mean of 26 points, (SD=6.2), in the AES-C and a mean of 28.1 points, (SD=6.4), in the AES-S.

The AES was validated in Chinese and German languages (Lee, Wen, Chao, Chen & Yen, 2008; Lueken et al., 2006). Lee et al. (2008) showed that the Chinese version of the AES-C had high internal consistency (Cronbach α=.90). For the Chinese sample of 31 normal individuals, a mean of 27.9 points, (SD=7.6), in the AES-C would identify apathetic patients. Lueken et al. (2006) reported high internal consistency for the German version of

the AES-C and AES-S (Cronbach $\alpha \geq .92$). In this German publication, based on data from 37 controls, participants would be apathetic if they scored a mean of 20.2, (*SD*=2.7), in the AES-C, and a mean of 23.5, (*SD*=5.8), in the AES-S. The use of the AES was extended to neurologic and psychiatric disorders; Sagen, Faerden, Haug, Melle, Finset, & Dammen (2010) studied factor structure of the Norwegian version of the AES-S in 85 stroke patients and of the AES-C in 76 subarachnoid haemorrhage patients, and of both scales in 104 psychotic patients and Lane-Brown and Tate (2009) validated AES-C in 34 patients with severe traumatic brain injury.

More recently, Lueken et al. (2007) validated a short version of the AES, with items 1 to 4, 6 to 9, 17 and 18, in 356 demented nursing home residents. This short version identified apathetic patients if they had a mean of 14.7 points, (*SD*=9.8). Sagen et al. (2010) studied factor structure of a second 10-item version of the AES, with items 1, 2, 4 to 7, 9, 16 to 18, in the follow-up of stroke, subarachnoid haemorrhage and psychotic patients. However, these short versions were not adequate for patients in an acute hospital setting. In the Neurology Service of Hospital Santa Maria in Lisbon, we evaluate acute neurologic patients, and because some of the AES items are not appropriate for a context as a hospital ward for acute patients, we develop a new short version of the AES.

The first aim of this study was to analyze the metric properties of the clinical-rated and self-rated Portuguese version of the AES. The second aim of this study was to analyze the metric properties of a clinical-rated and self-rated 10-item version scale of the AES.

2. METHODS

2.1. Participants

We included two groups of participants which were a) caregivers of patients attending the Neurologic Outpatient Clinic (“Healthy participants”) aged between 18-80 years old, and b) subjects older than 60 years old from a Day Centre for the elderly (“Elderly participants”).

Inclusion criteria for “healthy participants” and “elderly participants” were: 1) independent in daily activities, 2) fluency in Portuguese and understanding the purpose of the study, 3) living anywhere in Portugal. Exclusion criteria for “healthy participants” and

"elderly participants" were the presence of any psychiatric disorder or of a cognitive impairment, based on the DSM-IV-TR clinical criteria (APA, 2002).

We also included two groups of patients that were: a) patients attending the Dementia Outpatient Clinic ("Dementia patients"), and b) patients attending the Psychiatric Outpatient Clinic ("Depression patients"), at the Hospital Santa Maria in Lisbon.

Inclusion criteria for "demented" or "depressive patients" were: 1) having an exclusive diagnosis of mild Alzheimer's dementia or of mild cognitive impairment for the "dementia group", or 2) having an exclusive diagnosis of major depressive disorder or of a dystimic disorder based on the DSM-IV-TR clinical criteria (APA, 2002) for the "depressive group", 3) fluency in Portuguese, 4) understanding the purpose of the study, 5) older than 50 years old for the "dementia group" and older than 18 years old for the "depression group", and 6) living anywhere in Portugal.

Both participants and patients were invited to participate in the study and gave their informed consent. The Ethics Committee of the Faculty of Medicine, University of Lisbon, approved the study.

Table 1. Demographic characteristics of "participants" and "patients" included in each group to evaluate the clinical-rated and self-rated versions of the AES

Variables	AES-C "Healthy participants" (*n*=156)	AES-S "Healthy participants" (*n*=143)	AES-C "Elderly participants" (*n*=40)	AES-C/AES-S "Dementia patients" (*n*=21)	AES-C/AES-S "Depression patients" (*n*=21)
Age					
Mean±*SD*	51.8±15.1	50.5±14.8	71.8±5.1	80.2±6.5	53.9±12.2
Median	51	49	71.5	82	54
Range	20-80	20-80	61-84	70-93	18-71
18-40 years (*n*)	41	40	0	0	3
41-65 years (*n*)	80	76	4	0	14
66-95 years (*n*)	35	27	36	21	4
Gender					
Female (*n*)	113	102	30	11	20
Male (*n*)	43	41	10	10	1
Educational level					
Mean±*SD*	8.4±4.7	9.0±4.5	6.6±3.6	9.2±6.4	7.3±5.2
Median	9	9	4	8	5
Range	0-21	0-21	4-16	0-21	3-21
≤9 years (*n*)	91	78	33	12	17
>9 years (*n*)	65	65	7	9	4

Mean±*SD*: mean±standard deviation. **AES**: Apathy Evaluation Scale-Clinical. **AES-C**: Apathy Evaluation Scale-Clinical. **AES-S**: Apathy Evaluation Scale-Self-rated. **AES-C-10**: 10-item Apathy Evaluation Scale-Clinical-10. **AES-S-10**: 10-item Apathy Evaluation Scale-Self-rated-10.

A total sample of 238 individuals voluntarily participated in this study and included 156 “healthy participants” and 40 “elderly participants”, 21 patients with “dementia” and 21 patients with “depression”. (Table 1)

As expected “elderly participants” and “dementia patients” were older than “healthy participants” and “depression patients” ($F(3,237)=47.1$, $p=.0001$; Bonferroni $p<.001$). Women formed the majority in the group of patients with “depression” and were less frequent in the group of patients with “dementia” ($\chi 2(3)=9.93$, $p=.02$).

2.2. Apathy Evaluation Scale

The AES is an 18-item scale developed by Marin et al. (1991). The clinical rate (AES-C) and self-rated (AES-S) versions of the AES have 18 items each. Responses to each item can be “Not at all characteristic” (4 points), “Slightly characteristic” (3 points), “Somewhat characteristic” (2 points) or “Very characteristic” (1 point). Items 6, 10 and 11, as negative sentences were scored as “Not at all characteristic” (1 point), “Slightly characteristic” (2 points), “Somewhat characteristic” (3 points) or “Very characteristic” (4 points). Marin et al. (1991) defined that a higher total score indicated greater severity of apathy, ranging from a minimum of 18 points and a maximum of 72 points.

AES: Adaptation to the Portuguese language

A professional translator translated the English version of the AES-C to Portuguese, and another professional translator translated this Portuguese version into English. The final Portuguese and the corresponding English translations were e-mailed to the original author (Prof. RS Marin) to obtain his approval (Appendix 1). The author approved the translation of the 18-item AES-C version.

Construction and adaptation to the Portuguese language of a short version of the AES

Most of the patients admitted to an acute care hospital have a short stay. During their hospitalization, patients cannot answer if they “do things”, if they like to “start” or “finish” things, because they have to follow the hospital routine and pathways of care. Therefore, we

excluded those items from the AES that we considered not to be appropriate for assessing apathy in an acute hospital setting (items 2, 3, 4, 5, 7, 8, 9 and item 16). For the adaptation of the 18-item scale into a 10-item version, we kept the same order of the items: item 1 was kept as item 1, item 6 was changed to item 2, 10 to 3, 11 to 4, 12 to 5, 13 to 6, 14 to 7, 15 to 8, 17 to 9, and item 18 to item 10. The items selected for the clinical-rated version (AES-C-10) were the same as those included in the self-rated version (AES-S-10). As in the Lueken et al. (2007) validation publication, we also excluded items 5 and 16 and as in the Sagen et al. (2010) validation publication we excluded item 3 and 8. Lueken et al. (2007) and Sagen et al. (2010) excluded items 10, 11, 12, 13, 14 and 15, but we retained these items because we thought that for acute patients "being interested" about and "understand" their medical condition, "getting excited" with good things, such as the improvement of their medical condition, and maintaining their interest in "friends" and in getting their attention during their stay in the hospital, would provide good information about their motivation, or about the possible presence of indifference or even about their engagement in getting healthier. The common items in the 3 versions of a short AES were item 1 (Interested in things), item 6 (Little effort in anything), item 17 (Has initiative) and item 18 (Has motivation).

2.3. Procedure

"Healthy" and "elderly participants", "dementia" and "depression patients" were interviewed by two psychologists who performed a psychological and cognitive evaluation. For this purpose, we used the clinical information from the Day Centre file of each "elderly participant" and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) to assess depression. The Mini-Mental State Examination (MMSE) (Guerreiro, Silva, Botelho, Leitão, Castro-Caldas & Garcia, 1994) was used to assess cognition in "healthy participants" and "elderly participants" and in "dementia" and "depression patients". After being assessed for apathy with the AES-C "participants" and "patients" filled in the AES-S. If the "participants" or "patients" could not read (due to vision problems or being illiterate) the psychologist would read the questions from the AES-S, asking for a No ("Not at all characteristic") or Yes response, and if Yes either "Slightly characteristic", "Somewhat characteristic" or "Very characteristic".

2.4. Statistical Analysis

Bivariate analyses, comparing scores between 2 or all 4 samples, among the "healthy", "elderly", "dementia" and "depression" samples of subjects, were performed using ANOVA (*F*) with Bonferroni adjustment and independent t-test (*t*). The correlation between continuous variables was performed using Pearson correlation (*r*) analysis.

The answers given by the sample of 156 "healthy participants" were used for additional statistical analysis: 1) Construct validity by factor analysis of principal components with Varimax rotation, the extraction of three factors (we forced number three) and inspection of the screen plot of rotation values. 2) Internal consistency or reliability evaluation using a) Cronbach Alpha (α) and b) Split-half reliability, where results would show good inter-item correlation if α>.65. 3) Standardization: the cut-off point, which was the highest value following the value obtained by the mean plus two standard deviations (Z-score: mean+2*SD*), as proposed by Streiner and Norman (2003). Apathy was present if subjects scored the value of the cut-off point or above. 4) Categorization of age in three age groups: young (18-40), middle aged (40-65) and older subjects (65-80). 5) Educational levels categorized in the three groups of mandatory school education: low educational level (≤4 years of school), mean education (5-9 years of school) and high education (≥10 years of school).

Analysis was performed using the SPSS software and a two-tailed *p*-value of ≤.05 was considered statistically significant.

3. RESULTS

3.1. Metric properties of the AES-C

We included the sample of 156 "healthy participants" which constituted a random sequential sample of individuals without any psychiatric or neurological disease or daily living activities and who were caregivers of users of Neurologic Outpatient Clinic.

Internal consistency coefficient was high with a Cronbach α=.82 and a Split-half α=.67 (Between the 18 items: $F(17,155)=27.55$, $p< .01$). For the principal component analysis (PCA) we did not exclude any items from the scale because they all had high

values of >.40. Item component distribution is similar to the original version. The three components (Kaiser Rule) accounted for 47.3% of the variance (Table 2).

Table 2. The three PCA (Kaiser Rule) for the 18-version of the AES-C and AES-S (Rotated Component Matrix)

AES-C		AES-S	
Component 1	Factor Loading	Component 1	Factor Loading
1. S/he is interested in things.	.72	1. S/he is interested in things.	.45
3. Getting things started on his/her own is important to him/her.	.51	3. Getting things started on his/her own is important to him/her.	.48
4. S/he is interested in having new experiences.	.83	4. S/he is interested in having new experiences.	.79
5. S/he is interested in learning new things.	.84	5. S/he is interested in learning new things.	.79
6. S/he puts little effort into anything.	.60	14. When something good happens, s/he gets excited.	.24
10. Someone has to tell her/him what to do each day.	.40		
17. S/he has initiative.	.53	17. S/he has initiative.	.63
18. S/he has motivation.	.54	18. S/he has motivation.	.63
% of Variance	20.17	% of Variance	16.05
M score±*SD*	10.97±3.49	*M* score±*SD*	10.67±2.98
α	.82	α	.74
Component 2	Factor Loading	Component 2	Factor Loading
2. S/he gets things done during the day.	.43	2. S/he gets things done during the day.	.39
7. S/he approaches life with intensity.	.51	7. S/he approaches life with intensity.	.55
8. Seeing a job through to the end is important to her/him	.49	8. Seeing a job through to the end is important to her/him	.68
9. S/he spends time doing things that interest her/him.	.57	9. S/he spends time doing things that interest her/him.	.64
12. S/he has friends.	.66	12. S/he has friends.	.66
13. Getting together with friends is important to her/him.	.63	13. Getting together with friends is important to her/him.	.62
16. Getting things done during the day is important to her/him.	.62	16. Getting things done during the day is important to her/him.	.62
% of Variance	15.55	% of Variance	16.18
M score±*SD*	9.60±2.29	*M* score±*SD*	9.94±2.7
α	.68	α	.73
Component 3	Factor Loading	Component 3	Factor Loading
11. S/he is less concerned about her/his problems than s/he should be.	.78	11. S/he is less concerned about her/his problems than s/he should be.	.65
14. When something good happens, s/he gets excited.	.56	6. S/he puts little effort into anything.	.41
		10. Someone has to tell her/him what to do each day.	.59
15. S/he has an accurate understanding of her/his problems.	.73	15. S/he has an accurate understanding of her/his problems.	.66
% of Variance	11.55	% of Variance	10.41
M score±*SD*	3.62±1.03	*M* score±*SD*	6.0±1.9
α	.59	α	.52

AES-C: Apathy Evaluation Scale-Clinical, **AES-S**: Apathy Evaluation Scale-Self-rated

The three components were inter-correlated (Table 3). AES-C was highly correlated with components 1 and 2 and moderately correlated with component 3 (Table 3).

Table 3. Pearson's correlation (*r*) among the three components and between each of these and the AES, in the "healthy Participants" sample (*n*=156)

	Clinical			*Self-rated*		
Components	2	3	AES-C	2	3	AES-S
1	.37	.31	.89	.41	.38	.83
2		.14	.71		.32	.77
3			.47			.62

AES-C: Apathy Evaluation Scale-Clinical; **AES-S**: Apathy Evaluation Scale-Self-rated. *P*-values of <.01.

There were no differences in AES-C scale scores between genders ($t(154)=0.33$, $p>.05$) and among the three age groups ($F(2, 155)=1.94$, $p>.05$). There was a weak negative correlation between AES-C and educational level ($r=-.32$, $p<.01$) and we found some differences ($F(2,155)=11.54$, $p<0.01$; Bonferroni $p<.03$) among the three educational groups, with the lowest (≤4 years and 5-9 years of school) educated groups having higher cut-off points on the AES-C (Table 4).

Table 4. Cut-off points of the AES-C and AES-C-10, based on educational levels, in the "healthy Participants" sample (*n*=156)

Years of Education	**n**	**AES-C**				**AES-C-10**			
		Mean	*SD*	Z-score	Cut-off point	Mean	*SD*	Z-score	Cut-off point
≤4 years	56	26.27	5.46	37.19	38	13.16	2.77	18.70	19
5-9 years	35	24.77	6.10	36.97	37	12.83	2.94	18.71	19
≥10 years	65	21.98	3.68	29.34	30	11.82	2.05	15.92	16
Total	156	24.15	5.29	34.73	35	12.53	2.59	17.71	18

AES-C: Apathy Evaluation Scale-Clinical, **AES-S**: Apathy Evaluation Scale-Self-rated; ***SD***: Standard deviation

The cut-off point for the AES-C, independently of educational level, was 35 (Table 5) and participants scoring above would be considered as being apathetic (Eleven (5.1%) participants scored above.

Table 5. Metric characteristics of the AES and AES-10

	"Healthy participants" (*n*=156)	"Healthy partic pants" (*n*=143)	"Elderly participants" (*n*=40)	"Dementia patients" (*n*=21)	"Dementia patients" (*n*=21)	"Depression patients" (*n*=21)	"Depression patients" (*n*=21)
AES (18-Item Version)	**AES-C**	**AES-S**	**AES-C**	**AES-C**	**AES-S**	**AES-C**	**AES-S**
K-S (*p*-value)	1.84 (.002)	1.55 (.02)					
Mean±*SD* (score)	24.2±5.3	26.5±6	19.3±1.1	44.7±12.1	34.6±10.4	32.5±11.6	32.8±10.3
Mean+*2SD* (score)	34.8	38.6	21.5	68.9	55.4	55.7	53.4
Cut-off point (score)	35	39	22	69	56	56	54
Median (score)	23	26	19	41	33	29	29
Range (score)	13-44	18-49	18-22	24-64	20-59	19-65	22-56
Skewness	1.26	1.0					
AES (Short version)	**AES-C-10**	**AES-S-10**	**AES-C-10**	**AES-C-10**	**AES-S-10**	**AES-C-10**	**AES-S-10**
K-S (*p*-value)	2.28 (0.001)	1.47 (0.027)					
Mean±*SD* (score)	12.5±2.6	14.7±3.3	10.2±0.4	23.9±6.6	18.4±5.5	15.3±4.0	17.9±5.4
Mean+*2SD* (score)	17.7	21.3	11	37.1	29.4	23.3	28.7
Cut-off point (score)	18	22	11	37	30	24	29
Median (score)	12	14	10	24	18	15	16
Range (score)	10-22	10-26	10-11	12-34	12-30	10-26	12-29
Skewness	1.40	0.70					

AES-C: Apathy Evaluation Scale-Clinical; **AES-S**: Apathy Evaluation Scale-Self-rated; **AES-C-10**: 10-item Apathy Evaluation Scale-Clinical-10; **AES-S-10**: 10-item Apathy Evaluation Scale-Self-rated-10; **K-S**: Kolmogorov-Smirnov test; **Mean+*2SD***: Z-score which is the mean plus two standard deviations.

3.2. Metric properties of the AES-S

From the 156 "healthy participants" we included 143 for analysis of the AES-S. The remaining 13 "healthy participants" were not included because they refused to fill in the AES-S. (Table 1)

Internal consistency coefficient was high (Cronbach α=.81; Split-half=.60; Between the 18 items: $F(17, 142)= 8.56$, $p<.01$). We computed PCA (Kaiser Rule) with three

components and no item was excluded. The three components accounted for 42.6% of the variance (Table 2). The three components were correlated among each other. AES-S was moderately correlated with component 3 and it was highly correlated with components 1 and 2 (Table 3).

No differences were found in AES-S scale scores between genders ($t(141)=1.89$, $p>.05$) and among three age groups ($F(2,142)=0.41$, $p>0.05$). No correlation was found between AES-S scale scores and educational level ($r=-0.81$, $p>.05$) was find.

For the total AES-S scores (Table 5) the cut-off point was 39, thus "healthy participants" scoring 39 or more would be considered as apathetic (Six (4.2%) "healthy participants" were apathetic).

3.3. Metric properties of the short versions of the AES: AES-C-10 and AES-S-10 (Table 5)

For the AES-C-10 and the AES-S-10, we performed the same analysis but independently from the metric analysis made for AES-C and AES-S, using the "healthy participants" sample ($n=156$).

3.4. Metric properties of AES-C-10

Internal consistency coefficient for the AES-C-10 was high (Cronbach $\alpha=.70$; Split-half=.79). The PCA (Kaiser rule) with three components explained 58.6% of the variance of the 10 items. For AES-C-10, component 1 explained 23.4% of the variance and was represented by five items from the 18-item-scale version, namely: item 1 (interested in things), 6 (put little effort into things), 10 (someone has to tell what to do), 17 (has initiative) and 18 (has motivation). Component 2 explained 18.6% of the variance and was represented by three items: item 11 (less concerned about her/himself), 14 (get excited with good things) and 15 (accurate understanding of problems). Component 3 explained 16.5% of the variance and was represented by two items: item 12 (has friends) and 13 (to be with friends is important). Components 1 and 2 were moderately correlated ($r=.39$, $p<.01$), but components 1 and 3 ($r=.14$, $p>.05$) and components 2 and 3 ($r=.05$; $p>.05$) were not correlated. The AES-C-10 was positively correlated with the three components (F1: $r=.83$; F2: $r=.66$; F3: $r=.53$; $p<.01$).

There were no statistical differences in AES-C-10 scale scores between genders ($t(154)=0.04$, $p>.05$) and among the three age groups ($F(2, 155)= 0.33$, $p>.05$). There were differences ($F(2, 155)=4.55$, $p<.01$; Bonferroni $p<.01$) among the three educational groups (Table 4), with the lowest (≤4 years and 5-9 years of school) educated groups having higher cut-off points on the AES-C-10. The cut-off point for the AES-C-10, irrespective of educational level, was 18 points. Eleven (7.1%) "healthy participants" scored ≥18 and were considered as being apathetic.

3.5. Metric properties of AES-S-10

Internal consistency coefficient for the AES-S-10 was good (Cronbach $\alpha=0.65$; Split-half=0.57). The PCA (Kaiser rule) with three components explained 51.7% of the variance of the 10 items. For AES-S-10, component 1 explained 19.8% of the variance and was represented by items 1 (interested in things), 17 (has initiative) and 18 (has motivation). Component 2 explained 16.1% of the variance and was represented by items 6 (put little effort into things), 10 (someone has to tell her/him what to do), 11 (less concerned about her/himself), 14 (get excited with good things) and 15 (accurate understanding of problems). Component 3 explained 15.7% of the variance and was represented by items 12 (has friends) and 13 (to be with friends is important). Component 1 was mildly correlated with component 2 ($r=.35$, $p<.01$) and with component 3 ($r=.19$, $p<.05$). Correlation between components 2 and 3 was not significant ($r=.15$, $p>.05$). This AES-S-10 was positively correlated with each of the three components (F1: $r=.73$; F2: $r=.83$; F3: $r=.49$; $p<.01$).

For AES-S-10 scale scores there were no differences between genders ($t(141)=1.89$, $p>.05$), among the three age groups ($F(2, 142)=0.61$, $p>.05$) or among the three groups of educational level ($F(2, 142)=0.28$, $p>.05$). The cut-off point for the AES-S-10 was 22 points and in our sample of "healthy participants" 5 (3.5%) reported apathy.

3.6. Correlation between scales

The correlations between the scores in the four versions of the AES showed significant moderate to high values (Table 6).

Considering the clinical versions, the AES-C and the AES-C-10, the two were highly correlated meaning that the 10-item short version of the AES-C can easily substitute the AES-C in the clinical rate of apathy.

The same high correlation was seen between the two self-rated versions of the AES, the AES-S and the AES-S-10, meaning that AES-S-10 can replace the AES-S in the self-rating of apathy.

Table 6. Correlations between the two versions of the AES and the two versions of 10-item of the scales, in the "healthy participants" samples

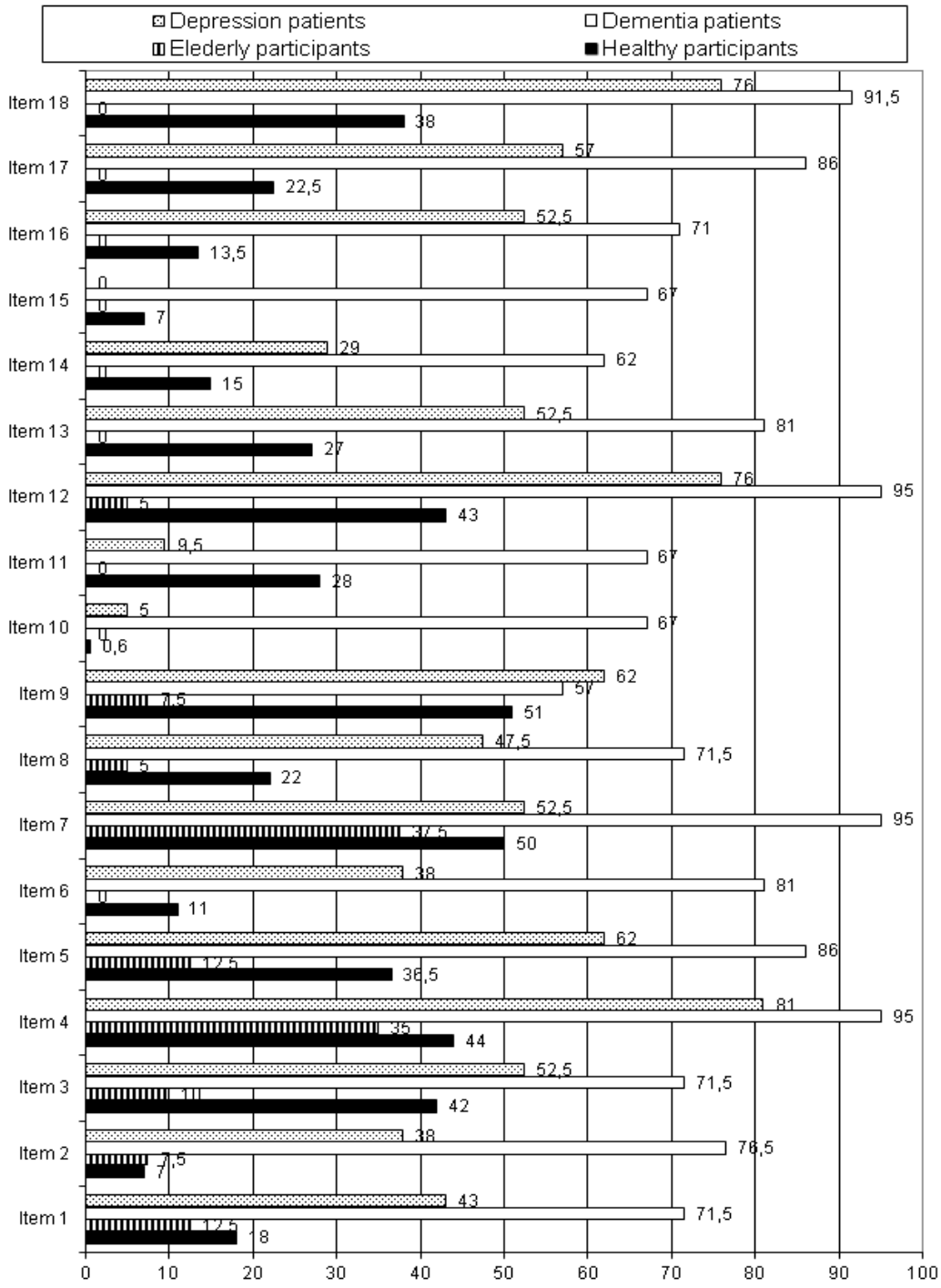
Scales	*AES-C*	*AES-C-10*	*AES-S-10*
AES-C	-	.89	
AES-S	.53	.39	.88
AES-S-10	.41	.36	-

p-values <0.01. **AES-C**: Apathy Evaluation Scale-Clinical; **AES-S**: Apathy Evaluation Scale-Self-rated; **AES-C-10**: 10-item Apathy Evaluation Scale-Clinical; **AES-S-10**: 10-item Apathy Evaluation Scale-Self-rated

3.7. Comparison between "participants" and "patients" samples: AES-C, AES-S, AES-C-10 and AES-S-10 (Table 1; Graphic 1)

Considering the AES, there were differences in: 1) AES-C: patients with "dementia" showing the highest mean score, followed by the group of patients with "depression" ($F(3, 237)=82.6$, $p<=.01$; Bonferroni: $p<.01$). "Dementia patients" scored positively most frequently in all items, followed by the group of "depression patients" (Graphic 1); 2) AES-S: "healthy participants" showed the lower mean scale score ($F(2, 184)=16.8$, $p<.01$; Bonferroni: $p<.01$); 3) AES-C-10: "Dementia patients" showed higher mean scale scores ($F(3, 237)=101.65$, $p<.01$; Bonferroni: $p<.01$); 4) AES-S-10: "Dementia patients" showed slightly higher mean scores compared with "healthy participants" and "elderly participants" ($F(2, 184)=12.97$, $p<.01$; Bonferroni: $p<.01$).

Graphic 1. AES-C profile of "participants" and "patients": Percentages of "participants" and "patients" scoring positively (Range 4-2 points: "Not at all" to "Somewhat characteristic") in each item.



In items 6, 10 and 11 all "elderly participants" scored "Not at all characteristic", and in items 13, 14, 15, 16, 17 and 18 all scored "Very characteristic", representing a percentage of zero "elderly participants" scoring positively, in both cases.

4. DISCUSSION

In this study of metric properties, the AES-C and the AES-S showed good construct validity and high internal consistency. The cut-off point of AES-C was 35 points. The cut-off point of the AES-S was 39 points. The items that loaded onto the ACP (Kaiser rule) for the AES-C and AES-S were quite similar, and both scales were moderately correlated. The short clinical-rated (AES-C-10) and self-rated (AES-S-10) short versions of the AES may be used instead of the long versions.

For this study, we included a sample of "healthy participants" of active community-dwelling Portuguese subjects. In order to have information on independent elderly subjects, we included a sample of "elderly participants" aged >60 years old. For a comparison with clinical samples, we included "depressive patients" and "demented patients". Comparisons among the four groups showed differences in mean scale scores in the AES-C and in the AES-S: "participants" presented lower mean scale scores compared with the two clinical samples. The "dementia patients" had the highest means scale scores. These results confirm previous publication showing that apathy is frequent in patients with "depression" and in patients with "dementia" (Biancosino, Picardi, Marmai, Biondi, M., & Grassi, 2010; Clarke, Ko, JLyketsos, Rebok, & Eaton, Mehta et al., 2008; 2010; Reyes, 2009).

Comparing our results with these three studies (Table 7) all reported good internal consistency with similar Cronbach α values. Both Chinese and English cut-off points were higher compared with the cut-off point in our study, but in the German version cut-off points were lower. The differences between our sample of "healthy participants" and the Marin et al. (1991) sample of normal controls could be higher motivation in the latter, as they were paid to participate in the study. Another difference was that our sample of "healthy participants" was more than 10 years younger compared with the other three samples, and had 4.7 mean years of educational level more than Marin et al. (1991) normal controls. Based on educational level, the cut-off points that we found for the AES-C were higher in "healthy participants" with low education level, and were quite similar to the cut-off point that we calculated for the Marin et al. (1991) sample. In our study, "healthy participants" with a low educational level expressed themselves and were clinically scored in their daily activities and interests more frequently as "not characteristic" or as "moderate", "mildly". On the other hand, "healthy participants" with higher educational levels expressed themselves and were clinically scored in their daily activities and interests more frequently as being "very characteristic". This was not the case on the AES-S, i.e. less educated "healthy participants" qualified and quantified their motivation, activity, curiosity and emotional attachment just the

same as “healthy participants” with higher educational levels. Clarke et al. (2007) highlighted the possibility of false negatives using the AES-S particularly for patients who have a lack of insight into their problems or apathy, which could be present because of the moderate (and not high) correlation between AES-C and AES-S.

Table 7. Descriptions of “healthy participants” included in the English, Chinese, German and Portuguese studies of the AES-C and AES-S. Internal consistency and cut-off point of each version.

	Marin et al., 1991	Lee et al., 2008	Lueken et al., 2006	Caeiro et al.
Sample of normal controls	31 participants Mean age= 68.3±5.7 years old Mean educational level=3.8	31 participants Mean age= 69±6.2 years old	37 participants Mean age= 69±6.2 years old	157 participants Mean age= 51.8±15.1 years old Mean educational level=8.4±4.7
Internal Consistency	AES-C: α=.90 AES-S: α=0.86	AES-C: α=.90	AES-C: α=.95 AES-S: α=0.92	AES-C: α=.82 AES-S: α=0.81
AES-C				
Z-score (Mean+*SD*)	38.4 26+6.2	39.6 24.4+7.6	25.6 20.2+2.7	35.1 24.5+5.3
Cut-off point	39	40	26	35
AES-S				
Z-score (Mean+*SD*)	40.9 28.1+6.4	- -	35.1 23.5+5.8	38.6 26.5+6
Cut-off point	41		35	39

AES-C: Apathy Evaluation Scale-Clinical; **AES-S**: Apathy Evaluation Scale-Self-rated

In the Clarke et al. (2008) publication, older patients with dementia (*n*=121; age mean=73.7, *SD*=9.4 years old) were apathetic if they scored above 40.5 points for the AES-C, and 36.5 points for the AES-S, which are lower than the cut-off point in our sample of patients with “dementia”.

We also studied the metric properties of a new 10-item short version of the AES clinical rate and of a self-rated scale, the AES-C-10 and the AES-S-10, to be used in acute hospital settings. The analysis of AES-C-10 (Cronbach α=.70; Split-half=.76) and the AES-S-10 (Cronbach α=.65; Split-half=.57) showed good construct validity and internal

consistency. The cut-off point of AES-C-10 was 18 points and the cut-off point of AES-C-10 was 22 points.

Lueken et al. (2007) also developed a short version of the AES-C, which is different from our short version of the AES-C. We chose and validated 10 items suitable for an acute setting, while Lueken et al. chose 10 items and validated a 10-item scale appropriate for demented nursing home residents and not an acute hospital setting. Sagen et al (2010) also performed a study of the metric properties of a second 10-item version of the AES, in stroke, subarachnoid haemorrhage and in psychiatric patients, 4 months after disease onset. Once again, we think that this proposal was not suitable for acute hospital settings. A common feature is that both were validated in patients and not in healthy participants as we did.

Our study had some limitations. We did not evaluate a sample of patients diagnosed as apathetic by DSM-IV-TR clinical criteria of Personality Disturbances Secondary to a Medical Condition on clinical groups of patients. We also did not compare the performance on AES with a different validated apathy scale. We should note that there is no other validated scale to assess apathy in the Portuguese language. We did not analyze test-retest and inter-rater reliability.

If not detected, silently apathy interferes with individual's mental health decreasing well being and psychosocial involvement (Lamers, Westerhof, Bohlmeijer, ten Klooster, & Keyes, 2011), which is the main reason for giving special attention.

In conclusion, the AES-C and the AES-S were proved to be useful to assess apathy in the normal Portuguese-speaking population. The shorter versions of these two scales (AES-C-10 and AES-S-10) would be of value for use in a hospital setting and in such a setting it can be used instead of the long-versions. Clearly, the four versions of the AES differentiated healthy common people from clinical samples.

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Appendix 1

Escala de Avaliação da Apatia

(Observação Clínica)

Nome do Doente: _____

Idade: _____ Data da Avaliação: _____

INSTRUÇÕES:

Eu vou-lhe perguntar uma série de questões acerca dos seus pensamentos, sentimentos e actividades. Para responder baseie-se nas últimas 4 semanas (1 mês).

Para iniciar fale-me acerca dos seus interesses actuais. Fale-me sobre qualquer coisa que seja do seu interesse, como por ex. hobbies, trabalho; actividades nas quais esteja envolvido ou que gostaria de fazer; interesses que possa ter dentro de casa ou fora dela, sozinho ou acompanhado; interesses que possa não executar, mas que são do seu interesse (ex.: nadar mesmo que seja Inverno).

"Agora gostaria que me contasse a sua rotina diária: Comece desde que acorda e se levanta até ao momento em que se deita."

1. Ela/Ele está interessada(o) nas coisas

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

2. Ela/Ele faz coisas durante o dia.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

3. Começar a fazer coisas é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

4. Ela/Ele está interessada(o) em ter novas experiências.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

5. Ela/Ele está interessada(o) em aprender coisas novas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

6. Ela/Ele esforça-se pouco nas coisas que faz.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

7. Ela/Ele vive a vida com intensidade.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

8. Acabar uma tarefa é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

9. Ela/Ele passa o tempo fazendo coisas que o interessam.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

10. Alguém tem que lhe dizer o que fazer em cada dia.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

11. Ela/Ele está menos preocupada(o) com os seus problemas do que deveria estar.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

12. Ela/Ele tem amigos.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

13. Estar com amigos é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

14. Quando acontece alguma coisa boa, ela/ele fica emocionada (o).

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

15. Ela/Ele tem compreensão adequada acerca dos seus problemas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

16. Ter as coisas feitas durante o dia é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

17. Ela/Ele tem iniciativa.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

18. Ela/Ele tem motivação.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

TOTAL:

Cotação:
Número de interesses manifestos;
Grau de detalhes verbalizados, para cada um dos interesses;
Aspectos afectivos da expressão verbal e não verbal.

Quantificação:
De modo nenhum: 0 itens
Minimamente: 1-2 itens
Moderadamente: 2-3 itens
Muito: 3 ou mais itens

Escala de Avaliação da Apatia

(Observação Clínica - Versão Reduzida)

Nome do Doente: _____

Idade: _____ Data da Avaliação: _____

1. Ela/Ele está interessada(o) nas coisas

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

2. Ela/Ele esforça-se pouco nas coisas que faz.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

3. Alguém tem que lhe dizer o que fazer em cada dia.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

4. Ela/Ele está menos preocupada(o) com os seus problemas do que deveria estar.

1 - Não é Característico	2 - Minimamente Característico	3 - Moderadamente Característico	4 - Muito Característico

5. Ela/Ele tem amigos.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

6. Estar com amigos é importante para ela/ele.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

7. Quando acontece alguma coisa boa, ela/ele fica animada (o).

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

8. Ela/Ele tem compreensão adequada acerca dos seus problemas.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

9. Ela/Ele tem iniciativa.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

10. Ela/Ele tem motivação.

4 - Não é Característico	3 - Minimamente Característico	2 - Moderadamente Característico	1 - Muito Característico

TOTAL:

Anotações: 1) Nº de interesses manifestos; 2) O grau de detalhes verbalizados, para cada um dos interesses; 3) Aspectos afectivos da expressão verbal e não verbal.

POST-STROKE APATHY

AN EXPLORATORY LONGITUDINAL STUDY

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Post-Stroke Apathy: An Exploratory Longitudinal Study

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ABSTRACT

INTRODUCTION: Post-stroke apathy is a disturbance of motivation evidenced by low initiative, difficulties in starting, sustaining or finishing any goal-direct activity, low self-activation or self-initiated behavior and emotional indifference. Apathy is a common behavioural disturbance in stroke survivors. We aimed at analysing the relationship between post-stroke apathy at 1-year after stroke and 1) apathy in acute phase; 2) demographic, pre-stroke predisposing conditions (previous mild cognitive impairment, alcohol abuse, mood/anxiety disorder) and clinical features (stroke type and location, neurological symptoms); 3) post-stroke depression and post-stroke cognitive impairment, and 4) post-stroke functional outcome, Quality of Life and the perception of Health.

METHODS: Consecutive stroke (infarct/intracerebral haemorrhage) patients without aphasia or consciousness disturbances were included in the acute phase of stroke and assessed at 1-year post-stroke. We assessed apathy with the clinical-rated version of the Apathy Evaluation Scale. We also assessed post-stroke depression (Montgomery Asberg Depression Rating Scale) and post-stroke cognitive impairment (attention, mental flexibility, verbal, motor and graphomotor initiative, and non-verbal and verbal abstract reasoning, and Mini-Mental State Examination), functional outcome (Barthel Index), Quality of Life and perception of Health (EuroQol). Data were analyzed using bivariate associations (Chi-square and t-test) and stepwise multivariate analysis (Odds Ratio: OR).

RESULTS: We included 76 stroke patients (32.9% of women, mean age of 62.9 years old (SD=10.9) and a mean of 6.9 (SD=4.3) of years of education). Apathy was present in 17 patients in the acute phase, and in 18 (23.7%) patients at 1-year post-stroke. At 1-year after stroke, 41% of the acute apathetic patients remained apathetic. Sixty-one percent of new cases of post-stroke apathy were detected. Post-stroke apathy was associated only with previous cognitive impairment, apathy in acute stroke, post-stroke cognitive impairment, verbal abstract reasoning and with worse Barthel Index scale scores. In the multivariate logistic regression model, verbal abstract reasoning (OR=7.03) and apathy in acute stroke (OR=3.8) were identified as independent factors for post-stroke apathy at 1-year. Apathetic patients did not report worse Quality of Life or Health.

CONCLUSION: Apathy in acute stroke phase was a reliable indicator of post-stroke apathy. Apathy should be assessed in both phases. Verbal abstract reasoning impairment was also an independent factor for post-stroke apathy impairing patients' ability to reason about goal-

direct activity. Even though apathetic patients had worse post-stroke functional outcome, they did not report losing Quality of Life or having worse Health.

1. INTRODUCTION

Post-stroke apathy is a disturbance of motivation evidenced by low initiative, difficulties in starting, sustaining or finishing any goal-directed activity, low self-activation or self-initiated behaviour and emotional indifference [1, 2]. Post-stroke apathy can be included in the DSM-IV-TR [3] criteria of Personality Change Due to Stroke, characterized by apathy and indifference.

Recent studies on post-stroke apathy were performed using validated apathy scales [4-8]. Post-stroke apathy is a disabling symptom present in 20% to 55% of stroke survivors [6 7, 9-15]. Post-stroke apathy has been associated with post-stroke cognitive impairment [6, 10, 12, 15, 16], and specifically with executive functioning impairment [6, 17-20], but not all studies supported that association [7, 11, 13, 14, 21-23].

In previous publications, post-stroke apathy and post-stroke depression overlapped at 3, 6 and 12 months' follow-up [6, 12, 13, 24] but not at 15-months' follow-up [6]. A review of the literature [25] and a systematic review [26] concluded that post-stroke apathy may be associated with post-stroke depression, but both can arise separately.

Several studies found an association between post-stroke apathy and poor functional outcome [9, 10, 12, 16, 22] or inability to return to previous occupational and social activities. However, a systematic review [26] did not confirm this association. Nonetheless, the quality of life of apathetic stroke patients and their perception about their own health was not previously studied.

Only two longitudinal studies [6, 10] reported the relationship between apathy in the acute phase of stroke with post-stroke apathy. In one of these the follow-up was performed by telephone interview [10].

For this study we operationalized the following research questions: 1) Is post-stroke apathy related to apathy in acute phase of stroke? 2) Is post-stroke apathy associated with age or with right-sided and subcortical lesion? 3) Is post-stroke apathy associated with post-stroke depression? 4) Is post-stroke apathy associated with post-stroke cognitive impairment? 5) Do post-stroke apathetic patients have a worse functional outcome, low Quality of Life and the perception of poor health in post-stroke phase?

2. METHODS AND MATERIAL

2.1. Sample

Between 2006 and 2008, we studied prospectively consecutive stroke patients (infarct or intracerebral haemorrhage). Patients in the acute phase of stroke were admitted to the stroke unit of the Neurology Department of an University Hospital. All patients performed a post-stroke neuropsychiatric and neuropsychological evaluation at 1-year follow-up. We obtained informed consent from all patients.

Following a previously described methodology [27] we excluded acute stroke patients who had a severe communication disturbance, defined as a score of 2-3 on the Neurological Institute Health Stroke Scale [28], items "Best Language" or "Dysarthria", and patients with a Glasgow Coma Scale [29] score below 9. We also excluded patients who did not perform the evaluation at 1-year follow-up.

In the acute phase, a neurologist (T.P.M., P.C. or J.M.F.) collected clinical and neuroimaging data. All patients had a CT or MR, including DWI, performed in the acute phase of stroke to define the location of the lesion. The location of stroke was categorized as 1) brainstem/cerebellum or hemispheric, 2) hemispheric left or right, 3) hemispheric subcortical, cortical or cortico-subcortical, 4) thalamic or striatocapsular [30]. If the stroke lesion could not be identified by neuroimaging we used clinical criteria (symptoms and signs) to classify the stroke as brainstem/cerebellum or hemispheric, and hemispheric left or right. Ischemic stroke was classified according to the Oxford Community Stroke Project classification (PACI, TACI, POCI and LACI) [31].

The following pre-stroke predisposing conditions for post-stroke apathy were considered: 1) mild cognitive impairment, defined as a medical diagnosis of mild cognitive impairment or a history of memory and another cognitive domain disorder with no functional impairment in daily living activities, confirmed by a proxy, 2) alcohol abuse, defined as 5 or more drinks daily, and 3) previous mood or anxiety disorder [3], defined if the patient had a previous diagnosis of a mood or anxiety disorder or if the patient had been either prescribed specific medication for these conditions and used it for more than a month.

At discharge, functional outcome was assessed with the modified Rankin Scale (mRS) [32]. Unfavourable outcome was defined as a mRS score ≥3 (death or dependency).

At 1-year follow-up we used the Barthel Index (range 0-100 points) [33] to assess the post-stroke functional outcome in daily living activities. To assess post-stroke Quality of Life

we used the EuroQol (range 0-10 points). EuroQol includes a self-rated perception of heath (Health self-rating) (range 0-100 points) [34].

2.2. Neuropsychiatric and Neuropsychological Evaluation

A trained psychologist (L.C.) performed an interview in the acute phase of stroke, whenever possible during the first 7 days after stroke onset. This interview aimed at collecting pre-stroke predisposing conditions and evaluate apathy in acute stroke. The same psychologist performed a neuropsychiatric and neuropsychological evaluation at 1-year follow-up.

2.3. Evaluation of apathy

Apathy was evaluated with the 18-item clinically rated version of the Apathy Evaluation Scale (AES-C/Clinical-Rated Apathy) [1]. This evaluation was performed in the acute phase of stroke and at 1-year follow-up. The AES-C cut-off points were used to define the presence of apathy, taking into consideration Portuguese educational levels [35]. An evaluation of self-rated apathy was performed using the self-rated version of the AES (AES-S/Self-Rated Apathy) [1]. The AES-S was used only for a comparison between clinical-rated and self-rated differences of post-stroke apathy; no other analyses were performed with the AES-S.

2.4. Post-stroke depression and post-stroke cognitive impairment evaluation

At 1-year follow-up, patients were diagnosed as having post-stroke depression if they fulfilled the DSM-IV-TR criteria for Mood Disorder Due to Stroke (Post-stroke Depression) [3] i.e., if they reported or displayed depressive mood and anhedonia, and scored ≥7 points in the Montgomery Asberg Depression Rating Scale [36, 37].

At 1-year follow-up, to assess post-stroke cognitive impairment we used the Mini-Mental State Examination (MMSE) [38]. The normative data of the Portuguese validation defined cut-off points taking educational levels into consideration [39]. We also assessed post-stroke executive functioning including attention (Trail Making Test A), mental flexibility (Trail Making Test B), verbal initiative (Verbal fluency-Food products), motor initiative

(Luria's alternate hand sequences), graphomotor initiative (Luria's alternating series), verbal abstract reasoning (Proverbs) and non-verbal abstract reasoning (Raven's Progressive Matrices Ab). We used normative data of the Portuguese validation for each test [40, 41]. Patients were classified as having impairment in a particular test when they scored 1.5 standard deviation [42-44] below the mean (for their age and educational level).

The Ethics Committee of the Faculty of Medicine, University of Lisbon, approved the study.

2.5. Statistics

Data was analyzed using IBM SPSS Statistics version 19. For categorical variables we used the chi-square ($\chi 2$), with continuity correction if necessary, and for continuous variables we used the independent t-test (t) to test bivariate associations. These statistical associations were performed between clinical-rated post-stroke apathy and gender, age (<65 years old or ≥65 years old), educational level (0-9 or ≥10 years of education), previous mild cognitive impairment, previous alcohol abuse, and previous psychiatric disorder, stroke type, stroke location and lateralization, apathy in acute stroke, post-stroke depression, post-stroke cognitive impairment, post-stroke executive dysfunctioning, mRS grade at discharge (0-2 or ≥3), Barthel Index, EuroQol and Health scores.

In order to find which variables were strongly associated with post-stroke apathy, we performed a multivariate analysis stepwise logistic regression model (Odds Ratio (OR) and Nagelkerke R Square (R^2)) for post-stroke apathy at 1-year follow-up, entering significant variables with a p≤0.15 [45] on the bivariate analysis.

A p-value ≤0.05 was statistically significant. No correction for multiple comparisons was performed [46].

3. RESULTS

3.1. Patients

Ninety-eight patients were included in the acute phase of stroke. Of these, 76 patients (77.7%) were assessed at 1-year follow-up (Table 1). There were no statistical

differences in gender ($\chi 2$=0.00, p=0.92), age (t=0.60, p=0.55), educational level (t=0.10, p=0.93), in previous mild cognitive impairment ($\chi 2$=0.52, p=0.77) and in apathy in acute stroke ($\chi 2$=0.02, p=0.90) between those patients who participated at 1-year follow-up and those who did not. Twenty-two patients were not assessed because 1 had died at the 6-months follow-up, 3 asked to be excluded from the study at 6-months, 4 asked to be excluded at 1-year follow-up, 14 missed the four appointments made for them to come to the re-evaluation at 1-year.

The sample of 76 patients included 25 (32.9%) woman, with a mean age of 62.9 years old (SD=10.9) and a mean of 6.9 (SD=4.3) of years of education. The remaining characteristics of the sample are depicted in table 1.

3.2. Relationship between post-stroke apathy and apathy in the acute phase of stroke

In the acute phase, 17 patients were clinically apathetic and of these 5 also self-reported apathy. Only one patient, of a total of six self-reporting apathy, was not clinically-rated as apathetic. Acute clinical-rated apathy and acute self-rated apathy were significantly associated ($\chi 2$=10.2; p=0.001).

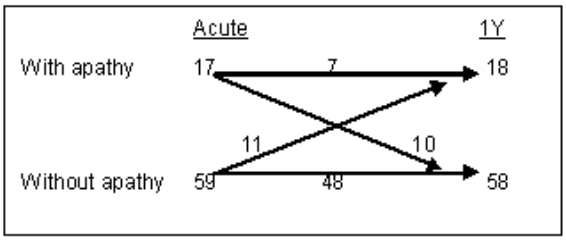
At 1-year follow-up, post-stroke apathy was present in 18 (23.7%) patients. Twelve (15.8%) patients self-reported post-stroke apathy. Only one patient self-reporting post-stroke apathy was not clinically-rated as apathetic ($\chi 2$=32.1; p=0.000). Of the 18 apathetic patients, 17 had severe apathy (Upper 5^{th} quintile of the AES-C scores distribution: AES-C≥37 points). Seven (41.2%) acute apathetic patients remained apathetic at 1-year follow-up (Figure 1). Eleven new cases of post-stroke apathy were identified at 1-year follow-up. Comparing the 7 patients who remained apathetic at 1-year follow-up with the 11 new cases of post-stroke apathy, we did not find any significant differences in demographic, clinical, acute and post-acute variables.

Table 1. Characteristics of the sample (n=76) and results of bivariate analysis

	Sample of participants N= 76		
	With Post-stroke apathy (n=18)	Without Post-stroke apathy (n=58)	Bivariate analysis, p-value
Age, ≥65 years old (n)	10	26	$\chi2$=0.63; p=0.42
Gender, Male (n)	13	38	$\chi2$=0.28; p=0.60
Educational level, 0-9 years (n)	17	45	$\chi2$=1.6; p=0.21
Previous alcohol abuse, (n)	4	7	$\chi2$=1.1; p=0.29
Previous psychiatric disease, (n)	5	23	$\chi2$=3.6; p=0.17
Previous mild cognitive impairment, (n)	**7**	7	**$\chi2$=7.3; p=0.03**
Stroke type, infarct (n)	16	46	$\chi2$=0.84; p=0.36
Stroke, right-sided (n)	7	24	$\chi2$=0.55; p=0.46
Stroke, left-sided (n)	9	20	
Stroke, hemispheric (n)	16	38	$\chi2$=2.6; p=0.11
Stroke, brainstem (n)	2	20	
Stroke, cortical (n)	2	5	$\chi2$=0.01; p=0.99
Stroke, subcortical (n)	10	23	
PACI (n)	7	12	
TACI (n)	2	7	$\chi2$=1.91; p=0.59
POCI (n)	4	18	
LACI (n)	3	9	
Apathy in acute stroke (n)	7	10	$\chi2$=2.5; p=0.11
Post-stroke depression (n)	5	14	$\chi2$=0.09; p=0.76
Post-stroke cognitive impairment in MMSE (n)	3	1	$\chi2$=3.5; p=0.06
Post-stroke attention impairment (n)	4	14	$\chi2$=0.0; p=1.0
Post-stroke mental flexibility impairment (n)	10	26	$\chi2$=2.1; p=0.15
Post-stroke verbal initiative impairment (n)	6	10	$\chi2$=2.1; p=0.14
Post-stroke motor initiative impairment (n)	4	11	$\chi2$=0.03; p=0.87
Post-stroke graphomotor initiative impairment (n)	2	2	$\chi2$=0.65; p=0.42
Post-stroke verbal abstract reasoning impairments (n)	**7**	5	**$\chi2$=7.3; p=0.007**
Post-stroke non-verbal abstract reasoning impairments (n)	4	4	$\chi2$=0.0; p=1.0
mRS at discharge, 0-2 (n)	10	42	$\chi2$=1.8; p=0.18
Barthel Index, Mean±SD	**85±25.8**	96.7±8.4	**t=3.0, p=0.004**
EuroQol, Mean±SD	2.2±2.0	1.7±1.7	t=1.0, p=0.31
Health, Mean±SD	6.1±1.6	6.6±1.8	t=1.1, p=0.28

(n): number of patients; **$\chi2$** (Chi-square test); **p** (p-value); **t** (Independent t-test); **MMSE** (Mini Mental State Examination); **mRS** (modified Rankin Scale); **Health** (Self-rated perception of heath)

Figure 1. Changes in the frequencies of apathy in the acute phase of stroke and at 1-year follow-up (76 patients)



Abbreviations: **Acute** (Acute phase); **1Y** (1-year follow-up)

3.3. Relationship between post-stroke apathy and age, pre-stroke predisposing conditions, stroke type and location

Post-stroke apathy was associated with previous mild cognitive impairment, but not with demographic or other predisposing conditions. No associations were found between post-stroke apathy and lesion location, in spite of a trend association with hemispherical location (88.9% of apathetic patients at 1-year had hemispheric lesion vs. 65.5% in non-apathetic patients; Table 1).

3.4. Relationship between post-stroke apathy and post-stroke depression and post-stroke cognitive impairment

At 1-year follow-up, no association was found between post-stroke apathy and post-stroke depression (Table 1).

Post-stroke apathy was associated with post-stroke verbal abstract reasoning disturbances and a trend association was found with global post-stroke cognitive impairment (Table 1).

3.5. Relationship between post-stroke apathy and functional outcome, Quality of Life or Health and perception of health

Post-stroke apathetic patients scored lower in the Barthel Index when compared with non-apathetic patients. Apathetic post-stroke patients did not report lower Quality of Life or Health. (Table 1)

3.6. Exploratory multivariate analysis: Independent factors for post-stroke apathy

We performed exploratory stepwise logistic regressions entering significant variables with a p≤0.15 on the bivariate analysis, to assess if they were independently associated with post-stroke apathy.

This model revealed that post-stroke verbal abstract reasoning (OR=7.03, 95%CI=1.4-33.3), and apathy in acute stroke (OR=3.8, 95%CI=0.97-14.9) were independently associated with post-stroke apathy at 1-year follow-up (R^2=23.3%, Area under curve=71%; Specificity=83.8%; Sensitivity=100%; Positive predictive value=21.4%; Negative predictive value=100.0%).

3.7. Analysis of the new cases of post-stroke apathy and risk factors

At 1-year follow-up, 11 new cases of post-stroke apathy were identified. The bivariate analysis with these 11 new cases (vs 65 non-new cases of post-stroke apathy) identified an association with post-stroke verbal abstract reasoning disturbances (χ2=4.1; p=.04). When we compared the 11 new cases of post-stroke apathy with the 48 patients who never presented apathy (either in the acute phase or in post-stroke phase) we only found an association with post-stroke verbal abstract reasoning disturbances (χ2=3.9; p=.05). Further analysis were performed comparing 4 groups of patients (7 who were apathetic in the acute and post-acute phase; 11 presenting only post-stroke apathy; 10 presenting only apathy in the acute phase; 48 who never had apathy), but the results were similar although results should be interpreted with caution because each of the subgroups had a modest size (eTable 2).

eTable 2. Characteristics of the sample (Four groups) and results on bivariate analysis

	Sample of participants N= 76				
	Apathetic only at the acute phase (n=10)	Apathetic only at the post-acute phase (n=11)	Apathetic at the acute and post-acute phase (n=7)	Never apathetic (n=48)	Bivariate analysis; p-value
Age, ≥65 years old (n)	4	6	4	16	$\chi2$=2.72; p=0.44
Gender, Male (n)	5	7	6	33	$\chi2$=2.54; p=0.47
Educational level, 0-9 years (n)	10	10	**7**	35	$\chi2$=9.84; p=0.20
Previous alcohol abuse, (n)	1	2	2	6	$\chi2$=1.37; p=0.71
Previous psychiatric disease, (n)	6	2	3	17	$\chi2$=4.18; p=0.24
Previous mild cognitive impairment, (n)	2	4	3	5	$\chi2$=6.55; p=0.09
Stroke type, infarct (n)	8	9	7	38	$\chi2$=3.05; p=0.38
Stroke, right-sided (n)	3	4	3	21	$\chi2$=1.85; p=0.61
Stroke, left-sided (n)	5	6	3	15	
Stroke, hemispheric (n)	7	10	6	31	$\chi2$=4.37; p=0.22
Stroke, brainstem (n)	3	1	1	17	
Stroke, cortical (n)	0	2	0	5	$\chi2$=4.35; p=0.63
Stroke, subcortical (n)	3	6	4	20	
Stroke, cortico-subcortical (n)	2	2	1	5	
PACI (n)	4	2	5	8	
TACI (n)	0	2	0	7	$\chi2$=15.19; p=0.09
POCI (n)	1	3	1	17	
LACI (n)	3	2	1	6	
Post-stroke depression (n)	2	3	2	12	$\chi2$=0.22; p=0.98
Post-stroke cognitive impairment in MMSE (n)	0	1	2	1	$\chi2$=6.54; p=0.09
Post-stroke attention impairment (n)	2	1	3	12	$\chi2$=2.53; p=0.47
Post-stroke mental flexibility impairment (n)	5	5	5	21	$\chi2$=4.27; p=0.23
Post-stroke verbal initiative impairment (n)	3	3	3	7	$\chi2$=3.68; p=0.30
Post-stroke motor initiative impairment (n)	3	2	2	8	$\chi2$=1.50; p=0.68
Post-stroke graphomotor initiative impairment (n)	1	1	1	1	$\chi2$=2.98; p=0.40
Post-stroke verbal abstract reasoning impairments (n)	1	**4**	3	4	**$\chi2$=8.28; p=0.04**
Post-stroke non-verbal abstract reasoning impairments (n)	3	2	2	10	$\chi2$=0.51; p=0.92
mRS at discharge, 0-2 (n)	7	5	5	35	$\chi2$=2.97; p=0.40
Barthel Index, Mean±SD	96.5±5.3	**86.4±26.7**	**82.9±26.3**	96.8±9.0	**F=3.00, p=0.04**
EuroQol, Mean±SD	2.4±2.3	2.6±2.0	1.6±2.1	1.6±1.7	F=1.40, p=0.25
Health, Mean±SD	6.1±2.0	6.2±1.7	5.9±1.5	6.7±1.8	F=0.72, p=0.54

(n): number of patients; **$\chi2$** (Chi-square test); **p** (p-value); **F** (ANOVA); **MMSE** (Mini Mental State Examination); **mRS** (modified Rankin Scale); **Health** (Self-rated perception of heath)

4. DISCUSSION

We aimed at studying the temporal evolution of apathy at 1-year after stroke and its relationship with apathy in acute stroke, demographic, pre-stroke predisposing conditions and clinical features (stroke type and location), post-stroke depression and cognitive impairment, and functional outcome, Quality of Life and Health. We found a frequency of 23.7% of post-stroke apathy. Of the patients with apathy in acute phase of stroke 41% remained apathetic at 1-year follow-up. Verbal abstract reasoning (OR=7.03) and apathy in acute stroke (OR=3.8) were independent factors for post-stroke apathy at 1-year follow-up. Post-stroke apathetic patients reported worse functional outcome.

In this study we had some limitations and bias inducers: 1) The inclusion of a sample of stroke patients of modest size; 2) The exclusion of 7 acute stroke patients with language disturbances (severe aphasia or dysarthria) may lead to a selection bias in relation to stroke lesion lateralization; 3) The loss of 22 patients during the follow-up, and 4) non-visualization of the acute stroke lesion, in two CT-scans, in 26 patients. These patients did not perform an MRI-scan, which limits the analysis of the role of the stroke lesion location in post-stroke apathy. The lack of a second MRI-scan at follow-up to search for new stroke events was also a limitation.

The first goal of our study was to identify if apathy in acute stroke predisposes to post-stroke apathy. We found a high frequency of post-stroke apathy, which is within the range of recent publications (20%-48.8% [7, 9, 10, 16, 47]). Forty-one percent of the patients with apathy in acute stroke remained apathetic at 1-year follow-up. Apathy in acute stroke increases the risk of post-stroke apathy by almost 4 times. This confirms previous findings from Mayo et al study [10]. Previously, Angelelli et al [14] had identified a three-fold risk of development of post-stroke apathy, at 6-months/1-year follow-up, in patients presenting apathy at 2-month follow-up. Eleven (61%) new cases of post-stroke apathy were identified at 1-year follow-up. No demographic or acute clinical variables were identified as risk-factors for new-cases of post-stroke apathy.

No associations were found between post-stroke apathy and acute demographic features or pre-stroke predisposing conditions.

Post-stroke apathy was not associated with any particular acute stroke location. Previously, 3 studies had associated post-stroke apathy with frontal lobe areas [13, 48, 49]. Considering the lateralization of the stroke, other publications found a relationship between

post-stroke apathy and right-sided cortical and subcortical lesions [12, 13, 50], left basal ganglia [16] and bilateral basal ganglia lesions [47].

We aimed at identifying the relationship between post-stroke apathy and post-stroke depression. As in some previous studies [10, 12], we did not find a statistical relationship between post-stroke apathy and post-stroke depression. The occurrence of depression is relatively the same between the apathetic and non-apathetic groups, corroborating previous studies [15]. Aybek et al [24] reported that 14% of patients with post-stroke apathy and depression share neuropsychological and neuroimaging findings. Jorge et al [25] reported 8% of coexistence of post-stroke apathy and depression. In our sample, 27.8% of the patients with post-stroke apathy also had post-stroke depression, which is higher than the previous studies.

We did not identify any relationship between post-stroke apathy and post-stroke cognitive impairment, which had been previously reported [51, 52]. Other studies reported a relationship between post-stroke apathy and cognitive impairment [6, 10, 12, 16]. At 1-year, post-stroke apathy was associated only with post-stroke verbal abstract reasoning impairments. In previous studies, post-stroke apathy was related to cognitive impairments, which included concentration, information processing speed and executive functioning impairments [6, 10, 12, 16, 18, 20, 22, 51].

Finally, the last goal was to find a relationship between post-stroke apathy and post-stroke poor functional outcome, Quality of Life and perception of Health. Patients with post-stroke apathy had worse functional outcome when compared with non-apathetic patients. Nevertheless, apathetic post-stroke patients did not report lower Quality of Life or of Health when compared with non-apathetic post-stroke patients. In two previous studies [6, 9, 10], post-stroke apathy had already been related to functional dependency. In a recent systematic review [26] it was showed that post-stroke apathy did not appear to have a negative impact on functional outcome. Additionally, from our study we may conclude that post-stroke apathetic patients did not evaluate worse functional outcome as a worsening in Quality of Life or of Health, when compared with non-apathetic patients.

5. CONCLUSION

Post-stroke apathy can be identified in 2 out of every 5 apathetic acute stroke patients. The assessment of apathy should be included in the evaluation performed in the acute and post-acute stroke phases. Post-stroke apathy is a neuropsychiatric disturbance independent of post-stroke depression. Post-stroke apathetic patients present verbal abstract reasoning impairments, which reduce their ability to find reasons for starting, sustaining or finishing any goal-direct activity. Although post-stroke apathy was related to poor functional outcome, apathetic patients did not see it as a loss in the Quality of Life or Health.

6. REFERENCES

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DISCUSSION

AND

CONCLUSIONS

APATHY IN ACUTE STROKE AND APATHETIC PERSONALITY DISTURBANCE SECONDARY TO STROKE

GENERAL DISCUSSION

In this thesis we investigated apathy secondary to stroke, in post-acute phase. We assessed a sample of stroke patients in the acute phase (until seven days after stroke onset) and at follow-up one year later (post-stroke phase).

We aimed at studying apathy at 1-year after stroke and its relationship with apathy in acute stroke, demographic, pre-stroke predisposing conditions and clinical (stroke type and location) features, and post-stroke depression, cognitive impairment, functional outcome, Quality of Life and Health.

Apathy is a disturbance of motivation evidenced by low initiative, difficulties in starting, sustaining or finishing any goal-directed activity, low self-activation or self-initiated behaviour and/or emotional indifference. Caregivers often describe patients as presenting loss of initiative, emotional indifference and a lack of concern, which only became apparent after stroke. This disturbance is defined by the DSM-IV-TR clinical criteria as Personality Change Due to Stroke-Apathetic Type [1].

In previous studies, apathy in the acute phase of stroke was a predictor of long-term post-stroke apathy. Stroke patients presenting post-stroke apathy at 2-month after stroke had a three time higher risk of development of post-stroke apathy at 6-months/1-year follow-up [2]. In a second study, over a 1-year period, 50% stroke survivors presented apathy [3]. In a third study, over a 15-months period [4], during follow-up 21.7% remained apathetic and 30.4% presented apathy and depression. Further studies are needed to confirm these findings. Several publications suggested that aging increases the risk of apathy in stroke patients [3-12].

Stroke involving subcortical areas of the cortico-subcortical circuits were associated with apathy [10, 11, 13], mostly if it was involved the cingulate gyrus [14], the posterior limb of the internal capsule [15], the head of the caudate nucleus [16], the lenticular nucleus or the globus pallidus or the striatum, substantia nigra, and the subthalamic nucleus [11, 12, 17], the anterior and medial thalamic nucleus [18-20]. Right-sided stroke lesions involving fronto-subcortical circuits or cortico-limbic-reticular subsystems, encompassing the fronto-subcortical regions [8-10, 14, 15, 18-21] caused apathy [7, 22-24] or indifference [25]. Bilateral lesions or left-sided stroke lesions at the corpus callosum and cingulate gyrus or at the superior frontal lobe area and basal ganglia, may present hypobulia or apathy or indifference [11, 12, 14, 17] or profound behaviour changes such as athymormia [26].

The presence of cognitive impairment before stroke was a risk factor for post-stroke apathy [8, 10]. Patients with post-stroke apathy had worse cognitive performances

compared with patients without apathy [4, 7, 8, 10, 12, 17]. Post-stroke executive-type dysfunctions, including attention and mental flexibility [8, 11, 26, 27-29], seems to be an important factor associated with post-stroke apathy [3, 4, 8, 18, 10-12, 30-34]. About a quarter to half of the samples of stroke patients presented an overlapping between post-stroke apathy and post-stroke depression [4, 8-11, 35]. In spite of a generalized acceptance of an association [13] between the two neuropsychiatric disturbances, some publications did not report any association between the two neuropsychiatric disturbances [8, 12], and the evidence was inconsistent. Apathy interferes with the ability of stroke patient to recovery his functional status [13], to seek out rehabilitation services and to carry out rehabilitation exercises [12, 36, 37] or return to social relationships [12, 33].

From our systematic review we concluded that the rate of apathy secondary to stroke (in acute and post-acute phases) range between a third to three-thirds of the stroke subjects. We also could confirm that age and cognitive impairment were associated with apathy secondary to stroke. We did not confirm that depression was associated with apathy secondary to stroke, in spite of the fact that apathetic patients present higher scores of depression. No strong associations were finding between apathy secondary to stroke and stroke location. Apathy secondary to stroke did not appear to have a negative impact on clinical global outcome.

In our main study on post-stroke apathy and its clinical associates, post-stroke apathy was present in almost a quarter (23.7%) of the stroke patients. Our multivariate model identified apathy in acute stroke and verbal abstract reasoning as independent factors for post-stroke apathy at 1-year follow-up. Apathy in the acute phase of stroke was a predictor of 41% of post-stroke apathy. Apathy in acute stroke increased the risk of post-stroke apathy by almost four-time fold. Nevertheless, 61% of the post-stroke apathy cases were identified only at follow-up. We confirmed that a particular cognitive domain such as verbal abstract reasoning was an important risk factor for post-stroke apathy. We did not confirm the relationship between post-stroke apathy and stroke location, depression and clinical outcome.

1. Systematic Review of Apathy Associated with Stroke

To start our research on post-stroke apathy we performed a systematic review to better estimate its rate and relationship with associated factors, as well as to explore if apathy was associated with poorer clinical outcome. (Chapter 3: *Apathy secondary to stroke: a systematic review and meta-analysis*)

For this review, post-stroke apathy was defined as a disturbance of motivation and an absence of feelings, emotions and/or interests as suggested by Marin and colleagues [38]. Cases of apathy were all considered for analysis provided that apathy was assessed with validated scales or through clearly defined criteria.

A total of 19 different stroke samples were included for analysis. Overall, the frequency of apathetic patients reported in individual studies ranged between 15.2 to 71.1%. The rates of apathy secondary to stroke found in our study are large, which could be due to the absence of a clear nosological definition, the phase (acute or post-acute) of stroke or due to the clinical criteria in each study. The mean age of included samples (range, 53 to 75 years old) was lower than that usually reported in hospital-based stroke samples, which could indicate the presence of selection bias in the included studies. Pooled rate of apathy secondary to stroke was 36.3% (95%CI 30.3 to 42.8%) with moderate heterogeneity (I2=46.8%). In the acute phase, the rate of apathy was 39.5%, and in the post-acute phase the rate was 34.3%. Apathy rate was significantly higher in any-stroke studies (41.6%; I2=44.9%) compared with studies including only first-ever strokes. We found high statistical heterogeneity (I^2≥50%) among the studies' results for stroke lesion lateralization and type, and for depression and clinical global outcome severity. The heterogeneity found in these outcomes was most probably due to differences in stroke phase (acute and post-acute phase), stroke history (first-ever and any-stroke), patients' age (younger and older) and study quality.

In the systematic review, apathetic patients were about 3 years older than non-apathetic patients without gender differences. The frequency of apathy secondary to stroke increased with age and was positively correlated with the presence and severity of cognitive impairment. Up to a quarter of non-demented community-dwelling elderly individuals have apathy (most without concomitant depression) [39, 40]. In the Ligthart et al [39] study, a past history of stroke or other vascular diseases were risk factors for apathy. Apathy is a common condition in older persons and in particular in older cognitively impaired people. Stroke is a risk factor for apathy in both.

The rate of "pure" apathy (without concomitant depression) was twice as frequent as the rate of "pure" depression (without concomitant apathy). Apathetic patients were more

frequently and severely depressed in comparison to non-apathetic patients. In previous reports, apathy was often associated with depression, but each one can occur separately from the other. Apathy and depression overlap longitudinally one year after stroke possibly indicating that cumulative vascular lesions are an important risk factor for both [4]. Apathy and depression share symptoms such as diminishing interest in daily activities and a decrease in motion activity. Patients with both neuropsychiatric disturbances after stroke share common neuropsychological features such as low MMSE scores [4] and working memory impairment [8]. Specific subcortical stroke locations can induce both apathy and depression [4, 8]

Rate of apathy secondary to stroke was similar for left and right-sided hemispheric stroke lesions and for ischemic and hemorrhagic stroke type. Specific stroke locations have been reported to be related to apathy namely basal ganglia lesions [11, 13] with possible involvement of the dopaminergic and glutamatergic systems [9, 35], anterior thalamic [18, 41] and polar-paramedian thalamic lesions [35], and amygdala lesions [42]. However, these statements are based on reports investigating apathy in patients with specific focal stroke location without controls and were not included in our systematic review.

Finally, apathy secondary to stroke did not appear to have a negative impact on clinical global outcome, except for apathetic patients with first-ever stroke and for younger patients. We would expected a negative impact of apathy in clinical global outcome, but our finding may be related to characteristics of apathy itself because apathetic patients may be less aware or report fewer complains about a loss of functionality.

In conclusion, apathy secondary to stroke is rather frequent, affecting 3 in every 10 stroke patients. Apathy is more frequent in patients with cognitive impairment or with depression, but pure forms of apathy can be present. With aging, apathy affects more subjects and with concomitant stroke lesion the rates increase. There was great heterogeneity among the studies on apathy secondary to stroke and related outcomes. Thus, further studies on the topic are needed.

2. The Metric Properties of the Apathy Evaluation Scale

One previous important preliminary study aimed at describing the metric properties of the clinical-rated and self-rated versions of the Apathy Evaluation Scale (AES) (Chapter 4: *Metric properties of the Portuguese version of the Apathy Evaluation Scale*), which would help to find cut-off points to define if a subject were apathetic. This purpose was the baseline for the achievement of goals 1 to 5 (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*), which were dependent on this one.

The Apathy Evaluation Scale was already validate for English, German and Chinese language populations. For our purpose, we studied a sample from the Portuguese community and two clinical samples.

We studied 156 healthy participants from the community, 40 healthy elderly participants from a day centre, 21 patients with dementia, and 21 patients with depression.

The study of the metric properties with the healthy sample of participants showed that the clinical-rated version of the AES (AES-C) (Cronbach α=.82; Split-half=.67) and the self-rated version of the AES (AES-S) (Cronbach α=.81; Split-half=.60) were reliable and valid instruments. The items that were loaded into the analysis of principal components for the AES-C and AES-S were quite similar. AES-C and AES-S were moderately correlated. The cut-off point of AES-C was dependent on the educational level (0-4 years of education= 38; 5-9 years=37; ≥10 years=30) and the cut-off point of the AES-S was 39 points.

The comparison among the four samples revealed that dementia patients had higher scores in the AES-C. For the AES-S, healthy participants scored themselves with the lowest mean scores.

As in the English, German and Chinese language versions, the Portuguese versions of the AES-C and AES-S showed good construct validity and high internal consistency. The Portuguese cut-off points were similar to English, German and Chinese language versions. Both are valid instruments to measure apathy in Portuguese-speaking individuals.

Additionally we performed a study of the metric properties of a 10-item version of the Apathy Evaluation Scale, clinical-rated (AES-C-10) and self-rated (AES-S-10) versions, to be used in acute stroke patients. Both versions were validated and can be used instead of the original versions of the Apathy Evaluation Scale.

3. Goals: Answers to Research Questions

The main findings on post-stroke apathy are reported in Chapter 5 (*Post-Stroke apathy: An Exploratory longitudinal study*), but here we will present the answers to each research question performed in the beginning of the thesis and discuss everyone.

For this main study, post-stroke apathy was defined as a disturbance of motivation and an absence of feelings, emotions and/or interests as suggested by Marin and colleagues [38]. Clinically, this disturbance is defined by the DSM-IV-TR clinical criteria as Personality Change Due to Stroke-Apathetic Type [1].

3.1. Is acute apathy associated with Personality Disturbance Secondary to Stroke-Apathetic-Type at 1-year?

For the first goal we aimed at describing the rate of post-stroke apathy at 1-year after stroke. Additionally, we aimed at finding the relationship between apathy in acute stroke and post-stroke apathy. (Chapter 5: *Post-Stroke Apathy: An Exploratory Longitudinal Study*)

In the study on post-stroke apathy, we identified 22.4% of apathy in acute stroke phase and 23.7% of post-stroke apathy at 1-year follow-up. In our multivariate statistical model, apathy in acute stroke (OR=3.8) was an independent factor for post-stroke apathy at 1-year follow-up. Another independent factor for post-stroke apathy was verbal abstract reasoning (OR=7.0) but this will be discussed later (Point 3.3.). At 1-year follow-up, 16.2% of the patients self-reported post-stroke apathy and only one of these was not clinical-rated as apathetic.

Apathy in acute stroke was a predictor of 41% of post-stroke apathy, that is, two-fifths of the patients with apathy in the acute stroke phase were apathetic at 1-year follow-up. Apathy in acute stroke increased the risk of post-stroke apathy almost four-fold. We confirmed what previous studies found [2] and that was that apathy in the acute phase of stroke was a predictor of long-term post-stroke apathy. In our study, the rate of patients that remained apathetic at follow-up was almost the double of the rate of patients remaining apathetic (21.7%) in the study performed by Withall [4].

Nevertheless, 61% of post-stroke apathy cases were identified at follow-up, which highlights the importance of the evaluation of apathy at follow-up.

In conclusion, we confirmed that post-stroke apathy is a frequent neuropsychiatric disturbance. We also confirmed that apathy in the acute phase of stroke increases the risk of post-stroke apathy.

3.2. Is Personality Disturbance Secondary to Stroke-Apathetic-Type associated with a specific acute stroke lesion location?

The second goal aimed at analysing the relationship between post-stroke apathy and a specific acute stroke location. (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

No associations were found between post-stroke apathy and stroke locations. We only found a trend involving an association between post-stroke apathy and hemispheric location. Lesions in the cerebellum or at the brainstem were not involved in motivation disturbances and were not related to post-stroke apathy. We did not confirm the association between post-stroke apathy and right-sided stroke location.

Based on previous publications [7-9, 12, 15, 17, 20, 23, 24, 41, 43], post-stroke apathy may be a dysfunction of the motivational/anterior cingulate network/system including the anterior cingulate circuit and fronto-subcortical connections. The anterior cingulate network/system also involves the coding of the emotional meaning of events and the coding of the direct influence of limbic signals during the process of coding. The network/system is also related to motor and cognitive inhibitions, which is related to other cortical and subcortical areas of the brain. A simple and focal strategic lesion on the anterior cingulate circuit may interfere with motivation [44-46].

We were not able to study the hypothesis that post-stroke apathy is a symptom of a damage of basal ganglia (anatomical structures included in fronto-subcortical circuits which comprise frontal cortical-basal-thalamic-cortical areas) or of the frontal-striatal-pallidal loops, especially lesions involving the limbic areas, when the medical cause is a stroke, could not be studied using our independent variable of stroke location (subcortical vs. cortical and left vs. right). In our systematic review there was not sufficient data to support conclusions to confirm that a circumscribed subcortical lesion was associated with post-stroke apathy. In the systematic the evidence of a right-sided stroke lesion being associated with post-stroke apathy was not confirmed. We could not confirm the association between post-stroke apathy and subcortical stroke location. However, it is known that apathy is frequent in other neurologic diseases, such as Parkinson disease, in which the involving of the basal ganglia

in recognized. However one fact became apparent that older patients presenting left-sided stroke lesions had a significantly higher rate of apathy (either acute or post-acute).

Our findings are in contradiction with previous data and this may be due to a limitation of our study, the lack of a variable describing a focal stroke location. Our study includes only generalized stroke locations such as hemispheric vs. cerebellum/brainstem, cortical vs. subcortical and left vs. right. The absence of MRI in 26% of our sample and the absence of a second CT to confirm the location of stroke had also limited our imaging data.

Nevertheless, we should highlight the age of our sample, which is about 15 years old lower than other samples included in previous studies. Younger samples may have less previous cerebral lesions of dysfunctions (known or silent) and may have less cognitive impairment after stroke, which may have implications on the rate of apathy.

3.3. Is Personality Disturbance Secondary to Stroke-Apathetic-Type associated with post-stroke cognitive and executive impairments?

The third goal of our study had the purpose to analyse the relationship between post-stroke apathy and post-stroke cognitive impairment. Additionally we search for the relationship between previous cognitive impairment and post-stroke apathy. (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

We found that, at 1-year follow-up, post-stroke verbal abstract reasoning impairment was an independent risk factor for post-stroke apathy, increasing the risk of post-stroke apathy by seven-fold. Global cognitive impairment (assessed with the MMSE) was not associated with post-stroke apathy. From our systematic review, in three publications studying global cognitive impairment apathetic patients were more often cognitively impaired.

Previous publications showed that post-stroke apathy was related to cognitive impairment [3] and in particular related to executive dysfunctions [18, 47-49]. Post-stroke apathy was associated with neuropsychological impairments in specific tasks such as verbal fluency [10], selective attention and mental flexibility [50].

For this study we did not base our neuropsychological evaluation on simple instruments such as MMSE, which is important for the triage of cognitive impairments but not for a formal and specific evaluation in the cognitive domain “executive functioning”. If we had chosen MMSE we would have concluded that post-stroke apathy was not associated

with cognitive impairment. We performed an extent evaluation of the "executive functioning" as reported in Chapter 5 (*Post-Stroke apathy: An Exploratory longitudinal study*).

We assessed verbal abstract reasoning with the "proverb interpretation" test. This test is one of the techniques used for "evaluating the quality or process of thinking more than the content of the response" [51, pp.603]. This test informs if a patient's thinking relies on an abstract or on a concrete dimension. Abstract reasoning ability is an important prerequisite for the use of prior learning in new contexts or for the way in which prior learning affects new learning and performance [52]. The improvement of abstract reasoning is important for patients who, due to brain lesion, have difficulties in their daily living activities [53].

Our study and others [8, 10] reported that previous cognitive impairments were associated with post-stroke apathy.

Saz et al [54] and Harris Y et al [55] showed that, in patients with vascular dementia, apathy as a behavioural symptom may be used to make the distinction between patients with and without dementia [56] or even be a predictor of dementia in patients with vascular dementia [55]. The association of post-stroke apathy and dementia represents a main determinant of nursing home admission and hospitalization in demented patients [56].

Thus, based on our results, the process of perceiving issues and reaching conclusions of apathetic stroke patients is not through the use of symbols or generalizations and abstraction. Instead, in these patients the process of think is through concrete factual processes of information with implications for the way patients deal with new contexts and new learning.

3.4. Is Personality Disturbance Secondary to Stroke-Apathetic-Type associated with post-stroke depression?

The fourth goal of our study was to perform an analysis of the relationship between post-stroke apathy and post-stroke depression. Additionally, we studied the association between previous psychiatric disturbances and post-stroke apathy. (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

From our study, post-stroke apathy was not associated with post-stroke depression, as was previously reported [17, 57, 58]. In our sample, post-stroke apathy and depression were present in a quarter of our patients, but in three quarters, the two clinical neuropsychiatric disturbances were independent. In our systematic review, apathetic

patients were more severely depressed mostly in the acute phase of stroke and for younger patients.

A previous publication [59] reported a frequency of 14% of patients with post-stroke apathy and post-stroke depression, and stressed the notion that the two can co-exist and share some anatomical structures, but they are not the same post-stroke neuropsychiatric disturbance. Hama et al. [17] found neuroanatomical differences between the two neuropsychiatric disturbances. These differences were the association between post-stroke depression with left frontal lobe lesions, and the association between post-stroke apathy with left or right basal ganglia lesions. More recently, Withall A et al [4] supported the idea that in elderly patients post-stroke apathy and depression overlap longitudinally due to cumulative vascular pathology.

What is usual in apathetic patients is that they show difficulties in starting and sustaining goal-direct activities, difficulties in thinking, low interest in things and an absence of deep emotions [38, 60]. Apathetic patients also may not care about losing interest, emotions or activity [38, 60], but depressive patients show predominantly anhedonia [28]. Depressive patients complains about their sadness and despair because they want to feel pleasure as they did prior to the event (the stroke), and they want to feel good emotions and the energy to do things as they used to before stroke and before depressive symptoms. These feelings are not common in apathetic patients [48]. Piamarta et al [28], interpreted these differences between apathy and anhedonia/depressive symptom as “different manifestations of a cognitive behavioural complex characterized by an inability to plan own actions, lack of motivation and inability to experience pleasure”.

3.5. Is Personality Disturbance Secondary to Stroke-Apathetic-Type associated with post-stroke functional outcome?

The fifth goal aimed at analysing the relationship between post-stroke apathy and late outcome. (Chapter 5: *Post-Stroke apathy: An Exploratory longitudinal study*)

We found a relationship between post-stroke apathy and bad functional outcome. Nevertheless, apathetic post-stroke patients did not report a loss in quality of life or in self-perception of health, when compared with non-apathetic post-stroke patients.

From previous publications we know that apathy in acute stroke was associated with a worse outcome at discharge [61] and that post-stroke apathy was a predictor of an unfavorable outcome following stroke [4, 62-64].

In our systematic review we did not confirm that apathetic patients had worse clinical global outcome, however there is a trend for patients with first-ever stroke and younger patients to present a poorer clinical global outcome.

Our data is in apparent contradiction with previous studies. This could be due to 1) stroke in our sample being less severe than in previous studies. 2) This could also be due to a lower mean age of our sample. Younger samples may present less apathy, less cognitive impairment, which all together may induce better clinical outcome, either because of the spontaneous improvement of stroke handicaps or because patients are more involved in their rehabilitation.

Interesting in our data is the contradiction of patients who had a bad outcome after stroke but who do not have the perception of having a loss in quality of life. This finding may indicate that apathetic stroke patients may have lost the perception of their own status.

CLINICAL IMPLICATIONS

We have found that post-stroke apathy may be clinically identified in the acute phase of stroke, using a scale validated for the acute stroke, in Portugal.

GENERAL LIMITATIONS

Our systematic review has several limitations. The results and conclusion are weakened by limitations inherent to meta-analysis and individual studies. Except for the rate of apathy (our primary outcome), a significant number of publications did not report data for other outcomes, in particular for the relationship between apathy and associated factors. Our analysis included only institution-based studies. Although our results are in close agreement with those from prospective community-dwelling populations' studies, they should be generalized with caution to the overall post-stroke population. The absence of a clear nosological definition, the phase (acute or post-acute) of stroke and the clinical criteria used in each study were limitations and bias when we estimated the rates of apathy secondary to stroke. Furthermore, in the studies included in the systematic review the authors used different scales to evaluate apathy, depression, cognitive impairment and clinical global outcome. None of the studies reported information about stroke severity, which may have had a negative impact on motivational status. The overall quality of included studies was moderate. However, reported quality for a few studies was low and selection and detection bias cannot be ruled out. The exclusion of publications written in languages than English, Spanish or French, as well as of non-published studies, may increase the risk of publication bias. Nevertheless, we were able to obtain non-published data from two studies and visual inspection of funnel plots shows symmetry, suggesting that publication bias was not a major drawback of our review.

Our study on the metric properties of the Apathy Evaluation Scale had some limitations. We did not evaluate a sample of patients diagnosed as apathetic by DSM-IV-TR clinical criteria of Personality Disturbances Secondary to a Medical Condition on clinical groups of patients. We also did not compare the performance on AES with a different validated apathy scale. We should note that there is no other validated scale to assess apathy in the Portuguese language. We did not analyze test-retest and inter-rater reliability.

In our principal study we also identified some limitations and bias. The first one is concerned with the sample. We included a sample of stroke patients of modest size. For a better generalization of our results it would have been important to include more than 98 acute stroke patients. Another limitation is related to the loss of 22% of the patients during the 1-year follow up. Finally, we excluded acute stroke patients with language disturbances (severe aphasia or dysarthria), which may have had lead to a selection bias in stroke lesion lateralization. The second limitation had to do with the non-inclusion of a systematic MRI evaluation of the stroke location. When we started the study the access to MRI was limited. Furthermore, the non-visualization of the acute stroke lesion, in two CT-scans, in 26 patients could have had lead to a bias in stroke location in association with apathy. These patients did not perform an MRI-scan, which limits the analysis of the role of the stroke lesion location in post-stroke apathy. The lack of a second MRI-scan at follow-up to search for new stroke events was also a limitation. Another limitation is the absence of information about stroke severity, which may have had a negative impact on motivational status.

CLINICAL AND RESEARCH IMPLICATIONS

Appropriate pharmacological therapeutic may be useful to treat post-stroke apathy. Pharmacological approaches should ideally be studied in a randomized trial. Only two clinical trials [65, 66] were performed to evaluate pharmacological approaches to apathy in stroke patients, but mostly case reports exist in the literature. From the experience of case-study reports, drugs with potential effect in improving apathy include: 1) Dopaminergic agents [67] such as amantadine, dopaminergic agonists (e.g. bromocriptine [68] and ropinirole [69]); 2) Stimulants, such as methylphenidate [70] and modafinil [71], because of its effect on stimulation of dopamine and norepinephrine release; 3) Antidepressants with dopaminergic (e.g. brupopion) or noradrenergic (e.g. venlafaxine); activity and 4) Acetylcholinesterase inhibitors (e.g. donepezil [65]] and nootropics [e.g. nefiracetam [66]). In one recent systematic review on post-stroke apathy data on two

Apathy is rather frequent in Alzheimer disease and it is a risk factor for poor outcome and higher mortality associated with delirium [72]. In Alzheimer disease the presence of neuropsychiatric symptoms is associated with a more frequent prescription of medication, mostly without prescription [73]. Modafinil has no great effect on the improvement of apathy in individuals with mild-to-moderate Alzheimer's disease [74] and caution should be taken in the use in stroke patients. Either from the experience of patients with Alzheimer or Parkinson disease treatment should not be restricted to psychoactive drugs, but should also include non-pharmacological techniques such as psychotherapy and occupational therapy [75].

A psychotherapeutic day hospital approach has been associated with a reduction of neuropsychiatric symptoms, better adhesion to therapeutic community treatment and with clinical progress in group therapy [56]. In demented apathetic patients, group therapy may be of great benefit to reduce apathy, which would be interesting to investigate in apathetic stroke patients.

Stroke is a frequent cause of long-term inability, and studies questioned the consequences of stroke in the relationship between patient and caregiver [76-80]. Some studies have shown the impact of patients' stroke on caregivers' mental health [76-81]. One of the consequences of personality changes secondary to stroke are feelings of a loss in the quality of life, by the patient and by the caregiver. The caregiver usually makes an effort in the establishment of a certain pattern of action and of emotions suitable for the patient's rehabilitation, which is of major importance for the success of rehabilitation [76-80]. Spouses of patients with stroke experienced a decline of social support over time and consequently

lose life satisfaction [82]. Caregivers suffering from social isolation may have benefits from therapeutic intervention in order to facilitate their social interactions and reduce the burden that they feel as caregivers. Thus, changes in the quality of life of caregivers are important topics to approach, specially related to post-stroke personality changes such as apathy.

It is known from the studies with Alzheimer disease patients that apathy is a risk factor for cognitive decline and for burden in caregivers [74, 82].

Moreover, the role of psychoeduational interventions and training rehabilitation techniques for the caregivers should be object of studies, It is important to inform the caregiver about a patient's loss of cognition and emotions and behavioral disturbances, as it is important to point out to the caregiver their own feelings of burden, anxiety and insecurities which should not be neglected [Wachters-Kaufmann C et al, 2005]. The informed caregiver should be prepared for the consequences of stroke, which may help in the patient's recovery and in the finding of new coping strategies dealing with the consequences of stroke. Nonetheless, some publications have highlighted an interest on drugs for patients to cure stroke instead of looking for coping strategies to deal with the consequences of stroke [Choi-Kwon S et al, 2005]. Training in rehabilitation settings, will make daily activities easier, reduce caregiver's burden and improve the quality of life of both the patient and of the caregiver [Kalra L et al, 2004].

Studies with consecutive patients with MRI performed in a non-acute phase should be made in order to find out focal stroke lesions responsible for post-stroke apathy.

Furthermore, future studies on post-stroke apathy should include information about stroke severity, which may have had a negative impact on motivational status.

In future studies, the evaluation of "executive functioning" type should also include the evaluation of mental flexibility assessed through the Stroop Color Test. This test is sensitive to dysfunction of the frontal lobe, with implications to the frontal-subcortical circuits. Dysfunction on these circuits is characterized by reduction of executive function, apathy and impulsive behaviour. Studies with stroke patients presenting executive dysfunction showed that patients had more often infarct lesion in the frontal lobe.

Additionally it would be important to study the association of post-stroke apathy to personal temperaments previous to stroke, aiming to study if depressive temperament predisposes to apathy.

CONCLUSIONS

In a systematic review and meta-analysis of studies on apathy secondary to stroke we found a moderate heterogeneity among the studies. In this meta-analysis a third of stroke patients presented apathy either in the acute phase or at 1-year follow-up. Apathy secondary to stroke was associated with cognitive impairment. In spite of the independency of post-stroke apathy and post-stroke depression, a quarter of the stroke patients present both neuropsychiatric disturbances. No conclusion could be drawn about the relationship between post-stroke apathy and stroke type/location or clinical/functional outcome.

One major independent risk factor for post-stroke apathy was apathy in acute stroke which predicted 41% of post-stroke apathy. Nevertheless, 60% of new cases of post-stroke apathy were reported. No stroke type or location was associated to post-stroke apathy. At 1-year follow-up verbal abstract reasoning was the only neuropsychological independent risk factor for post-stroke apathy. Post-stroke apathetic patients reported poor functional outcome more often.

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