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Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders

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Abstract

There is wide acknowledgement that apathy is an important behavioural syndrome in Alzheimer's disease and in various neuropsychiatric disorders. In light of recent research and the renewed interest in the correlates and impacts of apathy, and in its treatments, it is important to develop criteria for apathy that will be widely accepted, have clear operational steps, and that will be easily applied in practice and research settings. Meeting these needs is the focus of the task force work reported here.

The task force includes members of the Association Française de Psychiatrie Biologique, the European Psychiatric Association, the European Alzheimer's Disease Consortium and experts from Europe, Australia and North America. An advanced draft was discussed at the consensus meeting (during the EPA conference in April 7th 2008) and a final agreement reached concerning operational definitions and hierarchy of the criteria.

Apathy is defined as a disorder of motivation that persists over time and should meet the following requirements. Firstly, the core feature of apathy, diminished motivation, must be present for at least four weeks; secondly two of the three dimensions of apathy (reduced goal-directed behaviour, goal-directed cognitive activity, and emotions) must also be present; thirdly there should be identifiable functional impairments attributable to the apathy. Finally, exclusion criteria are specified to exclude symptoms and states that mimic apathy.

Keywords: Apathy; Alzheimer's disease; Neuropsychiatry; Diagnostic criteria

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1. Introduction

The word apathy, stemming from the Greek original *apatheia (derived from apathes – 'a' (without) + 'pathos' (feeling))* has undergone changes in meaning over the ages, and the modern construct presents apathy as a state of indifference or inertia, and as a disability or a maladaptive state. The semantic confusion related to shifts in meaning is one of the problems that have confounded the study of apathy in neuropsychiatry. Even today, confusion remains regarding the essential features of apathy and its boundaries with constructs such as aboulia, anhedonia, depression and learned helplessness. Consider, for example, that the Oxford English Dictionary defines apathy as a lack of interest or enthusiasm, an approach emphasizing a 'cognitive' dimension (interest) and a 'feeling' or 'emotional' dimension (enthusiasm). The same source defines aboulia (*from the Greek 'a' (without) + 'boule' (will)*) as a related concept that denotes absence of the will or power to generate focused action. In psychiatry, aboulia is considered by some to be a severe form of apathy [45]. Indeed, psychiatrists and neurologists responding to a survey considered aboulia to be a state characterized by difficulty in initiating and sustaining spontaneous movements, and reductions in emotional responsiveness, spontaneous speech, and social interaction [51], but also acknowledged that its status as a syndrome was controversial. The conceptualization of apathy noted in that study overlaps with the notion of apathy as a disorder of interest and enthusiasm, while also adding a 'motor' dimension (initiation and maintenance of movement) and a 'behavioural' dimension (social interaction).

Modern conceptualizations of apathy reflect efforts to reconcile the various dimensions of apathy. Despite differences, such as, for example, disagreements as to whether disturbances of motivation [29] or of initiative and self-generated voluntary and purposeful behaviour [48,26] are central features, most conceptualizations of apathy acknowledge that it is a syndrome in which all these dimensions are prominent (see Table 1). Another source of difficulty in the study of apathy (i.e., besides the semantic disagreements) is that the dimensions within the construct, such as motivation and interest, are latent variables so that their 'quality' and 'quantity' must be inferred by observing patient behaviour [16]. Fortunately, areas of agreement allow a common point of departure for the characterization and study of apathy. There is presently wide agreement that motivation, interest, action initiation and emotional reactivity are dimensions of apathy, and that lack of motivation is at the core of the disorder. An introspective dimension (lack of self-awareness, reflecting poor self-monitoring and self-management) is still debated. From this platform, Starkstein and colleagues have developed a set of diagnostic criteria for apathy [47], adapted from the work of Marin [28]; these criteria specify the following as core features of apathy: diminished motivation, initiative and interest, and blunting of emotions.

Table 1
Concepts of apathy

Author	Concept
Marin et al. [29]	Disorder of motivation with cognitive, sensory, motor and affective subtypes
Cummings et al. [13]	Disorder of interest or motivation; including lack of emotion, lack of initiation, lack of enthusiasm
Stuss et al. [48]	Disorder of initiative, manifesting lack of self-initiated action, which may be affective, behavioural or cognitive and includes "social apathy" – a disorder of sense of self and of social awareness
Robert et al. [42]	Disorder of motivation with emotional blunting, lack of initiative, lack of interest
Sockeel et al. [43]	Disorder of intellectual curiosity, action initiation, emotion and self-awareness
Levy and Dubois [53]	Disorder of voluntary and goal-directed behaviours; with three subtypes of disrupted "signal" processing: – emotional-affective, cognitive and auto-activation
Starkstein and Leentjens [45]	Disorder of motivation with diminished goal-directed behaviour and cognition

2. Why new criteria for apathy?

Broadly speaking, two principal reasons exist for formulating formal consensus criteria regarding apathy in dementia and neuropsychiatry: (1) recognition of its growing importance to neuropsychiatric research and practice, and (2) the need for reliable case description and identification, to facilitate communication, research and treatment. We review these issues below.

There is presently wide acknowledgement that apathy is an important behavioural syndrome in various neuropsychiatric disorders. Apathy is common in diseases such as Alzheimer disease, Parkinson's disease and associated dementias, frontotemporal dementias and stroke [25,49]. It is the most frequent neuropsychiatric symptom in AD [31,39] and in many other dementias, and presents at all stages of the disease (Table 2). In addition, apathy occurs as a stable syndrome in AD. Apathy in AD, or other dementias, is generally accompanied by heightened functional disability and by greater carer burden and stress [24,34].

Studies of the classification or clustering of neuropsychiatric symptoms in dementia, typically using the Neuropsychiatric Inventory (NPI) [13] for measurement, have consistently identified apathy as "classes" or "factors". For example, in the EADC (European Alzheimer's Disease Consortium) study [1], principal component analysis of cross-sectional data from 2354 patients with AD segregated four syndromes: hyperactivity, psychosis, affective and apathy. The apathy syndrome was the most common, occurring in almost 65% of the patients. A later analysis of data from the same sample provided indications of stability of the same syndromes across several neurodegenerative disorders, including vascular dementia, dementia with Lewy bodies and frontotemporal dementia [2]. Thus apathy is prominent among the neuropsychiatric complications of dementia, and is liable to co-exist with other disabling phenomena.

Table 2
Frequency of Neuropsychiatric symptoms evaluated with the NPI in 2 European studies with different cut off scores

NPI Domain	ICTUS study symptom present if NPI score >3			REAL study symptom present if NPI score >0	
	CDR 0.5: very mild, $N = 571$	CDR 1: mild, $N = 595$	CDR 2–3: moderate, $N = 179$	MMSE 21–30, $N = 244$	MMSE 11–20, $N = 255$
Delusions	3.85	10.1	19.6	10.2	24.7
Hallucinations	0.9	3.2	12.8	5.7	7.8
Agitation/aggression	9.3	16.6	27.4	32.8	44.3
Depression	18.4	23.9	33.5	36.9	42.7
Anxiety	15.9	22	29.6	44.3	46.3
Euphoria	12.6	2.6	6.5	4.5	9.8
Apathy	**18.4**	**39**	**48**	**47.9**	**63.5**
Disinhibition	3.5	5.6	17.3	10.2	13.3
Irritability	14.4	19	23.5	28.3	25
Aberrant motor behaviour	4.9	13.3	21.8	14.7	29.8
Sleep	9.6	13.8	22.9	13.5	12.9
Eating	7.36	14.8	22.4	20.5	24.3

NPI = neuropsychiatric inventory, CDR = clinical dementia rating, MMSE = mini mental state examination.
REAL: the multicenter PHRC REAL-FR cohort is a longitudinal study for community-dwelling patients with a diagnosis of AD. NPI was completed at study entry for 499 patients [29].
ICTUS – EADC: European Alzheimer Disease Consortium: the ICTUS study is an ongoing longitudinal prospective observational study of patients with Alzheimer's disease recruited in 29 centers in Europe. NPI was completed at study entry for 1345 patients [27].

There is also a growing body of evidence indicating that apathy is a prominent feature of pre-dementia states [27,10,37,18,22,34,6]. Indeed, there are indications that apathy may be predictive of later dementia [38]. One study of patients with mild cognitive impairment (MCI) found that the risk of conversion to AD was significantly higher for patients manifesting lack of interest, their main indicator of apathy [41].

Another important reason is the well-established overlap between apathy and depression. Although both conditions share common features, they are distinct and separable with careful measurement in dementia [25] and milder cognitive syndromes [34]. Older individuals who have apathy are more likely than those who have depression (and those who have neither condition) to have cognitive disorders [23,30]. Thus, formal criteria for the diagnosis of apathy can be expected to facilitate the recognition of apathy in elders, in turn increasing the likelihood of early identification of individuals with cognitive impairment or mild dementia. Furthermore, when apathy and depression co-occur, identification of apathy may be helpful in the interpretation of unsatisfactory treatment response and in the formulation of alternative treatment strategies.

In addition, establishment of consensus criteria may enhance the quality of clinical care for patients with dementia, since apathy may be a treatable condition. In a recent review of the literature on the efficacy of cholinesterase inhibitors in AD [14], it was reported that whilst many types of behaviour may be ameliorated, apathy, delusions and aberrant motor behaviour are the most likely to improve. Recently, clinical trials have provided indications that focused pharmacotherapy may be beneficial for apathy in Parkinson disease [15] and in dementia [20,35]. Apathy has also been a target of the non-pharmacological interventions [6,21,36].

In light of research developments and the renewed interest in the correlates and impacts of apathy, and in treatments, it is important to develop criteria for apathy status that will be widely accepted, have clear operational steps, and that will be easily applied in practice and research settings. Meeting these needs is the focus of the work reported in this paper.

3. Method

Under the auspices of the AFPB (Association Française de Psychiatrie Biologique) and the EPA (European Psychiatric Association), a task force was set up to revise the Starkstein criteria for apathy [47]. This task force was chaired by Philippe Robert and included members of the AFPB, EPA and the European Alzheimer's Disease Consortium (EADC), invited on the basis of their expertise in the neuropsychiatry of neurodegenerative diseases. The task force also included other experts from within Europe, and from Australia and North America.

A statement of goals and conceptual questions regarding proposed criteria for apathy in AD and other neurodegenerative diseases was circulated to members of the task force at the beginning of the process in December 2007. Following this, a succession of draft proposals were sent out between December 2007 and April 2008 for review, commentary and editing. An advanced draft of proposed criteria was reviewed and discussed at the consensus meeting (during the EPA conference in Nice, France, in April 7th 2008), during which outstanding conceptual and semantic issues were discussed and a final agreement reached concerning operational definitions and hierarchy of the criteria.

4. Revised criteria for apathy

The revised criteria (see Table 3) follow the same general structure as the criteria proposed by Sergio Starkstein and colleagues in 2001 [47]; firstly (A) a general statement on the

Table 3
Apathy proposed criteria

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D

A Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

B Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time

Domain B1 : Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
- Loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)

Domain B2 : Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).
- Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighbourhood or community)

Domain B3 : Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
- Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)

C These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

core feature of apathy being diminished motivation; secondly (B 1–3) a description of the three dimensions of apathy; thirdly (C) a requirement for functional impairments attributed to the apathy; and fourthly (D) specific exclusion criteria. Here, we explain the consensus reached by the task force for the revision of each section (A–D).

Apathy is a syndrome with three domains (B) the core feature being a loss or diminution of motivation (A). For a diagnosis of apathy the patient should fulfil each of the criteria A, B, C and D.

Criterion A stipulates loss of or diminished motivation, which may be reported by the patient or by observers who are familiar with the patient. This criterion defines apathy as a disorder of motivation. Consensus exists that loss of or diminution of motivation (relative to a lifelong level of functioning and the standards of the patient's age and culture) is central to virtually all modern definitions or conceptualizations of apathy (see Table 1), and that it should represent the core criterion for the syndrome of apathy, with its components (or ''specific symptoms'') further defined in Criterion B.

Criterion B indicates that apathy is generally a persistent state, rather than a transient or intermittent one by incorporating in the definition a minimum duration of four weeks, as suggested by Starkstein and Leentjens [45] in recent work. This criterion was added to differentiate from the transient states that may mimic the apathy of primary dementias, such as to occur during 'off' periods in Parkinson's disease patients, during hypo-arousal in delirium, and during acute emotional responses to stress.

Criterion B is also based on the premise that change in motivation can be observed (and measured) by examining a patient's responsiveness to internal or external stimuli. Each of the three domains within Criterion B (behaviour, cognition and emotion) includes two symptoms. The first symptom pertains to self-initiated or 'internal' actions, cognitions and emotions, and the second symptom to the patient's responsiveness to 'external' stimuli.

Domain B1, stipulates loss of or diminished goal-directed behaviour, specifically loss of self-initiated behaviour and loss of environment-stimulated behaviour. These were found to be the most frequently occurring features of apathy in a prospective European multi-centre study (ICTUS) that evaluated 216 AD patients for apathy, using the Apathy Inventory. This criterion is also based on the understanding that reductions in goal-directed behaviour affect routine (habitual) and non-routine (occasional) activities. The example 'communicating choices' identifies goal-directed prosocial behaviour, although there is a potential for its ascertainment to become confounded with executive functions such as decision-making.

Domain B2, referring to reduced goal-directed cognitive activity, is usually interpreted in practical terms as a loss of or diminished interest that is most often observed in leisure activities [50]. This domain indicates that the patient is less interested in the activities and plans of others, in friends and family members, or in their own usual leisure activities or professional interests. However, 'interest' arising from 'internal' stimuli is dependent on a number of factors relating to the individual, such as personality, culture and education. Conceptually, the affective aspects of interest, such as excitement, overlap with domain B3 (i.e., with goal-directed feelings, see below), thus introducing a potential source of ascertainment error (i.e., violation of the unstated assumption that domains B2 and B3 are independently ascertained). Therefore, an alternative

construct, 'curiosity', which appears more amenable to operationalization than interest, was adopted during the consensus process so as to focus the criterion more securely on the cognitive aspects of goal-directed behaviour.

Domain B3 focuses on the affective aspects of the lost or diminished motivation. It also incorporates the construct 'emotional blunting', which is widely used to describe the affective presentation of apathy. However, the challenge was how exactly to operationalize emotional blunting. The task force considered that in clinical practice 'emotional blunting' can manifest as reduction in a patient's capacity to express emotional reactions to everyday events. The task force also considered the issue of differentiating experienced and expressed affects, a distinction consistent with the approach taken in the structuring of domains B1 and B2. Since it is not clear that loss of 'experienced' emotion can be reliably ascertained or inferred, the approach undertaken was to substitute 'observed' for 'expressed' and 'self-reported' for ''experienced'' in laying out the domain B3.

Criterion C refers to functional impairment that is largely attributable to the symptoms specified in criteria A and B.

Criterion D is intended to exclude from definition conditions and states that mimic apathy, as well as transient states of apathy that can be attributed to a discrete non-neuropsychiatric cause. It is widely known that apathy (in neuropsychiatric disorders) frequently co-exists with other syndromes, especially depression. The task force emphasizes the importance of distinguishing apathy from depression in neuropsychiatric disorders (and from other co-existing syndromes), and notes that present-day measures of apathy and of depression facilitate the differentiation in practice and research – although none is entirely satisfactory.

5. Discussion and additional considerations

Although most of the members of the task force are involved in neuropsychiatry or old-age psychiatry, the task force is aware that apathy may also be a feature of non-dementia disorders such as major depression and schizophrenia.

For instance an important features of schizophrenia are negative symptoms [33]. They are characterized by the absence of normal levels of activation, initiative and affect [3] and therefore closed to apathy. A number of neurocognitive theories have been put forward to explain the common phenomenology of negative symptoms and apathy [52]. Frith [19] proposed that behavioural signs associated with negative symptoms could be understood in terms of a core deficit in the generation of willed action. Brown and Pluck [8] referred both apathy and negative symptoms to the general concept of goal-directed behaviour. On a behavioural point of view lack of initiative and interest, core dimensions of apathy, is close to ''wanting'' defined in animal studies as the underlying implicit motivational component of reward mediated by mesolimbic dopamine circuitry [5].

There are also striking similarities between the brain imaging profiles of negative symptoms in schizophrenia, melancholic depression [52] and apathy in AD or related disorders [49]. In AD functional brain imaging studies indicated that the most neuro-anatomical salient abnormalities related to apathy appear to be hypoperfusion and hypometabolism of anterior cingulate and related frontosubcortical structure [4,12,32].

The cingulate is a nexus that integrates the various components intended to lead to a goal-directed behaviour. It is the central part of a cortico–subcortical network and one of its main characteristics is the importance of afferences coming from different regions including frontal, vegetative and sensory processing regions. The cingulate cortex has been implicated in human clinical conditions such as depression, pain and distress [17], attention [11], reward [7] and is part of an executive control network, working in tandem with prefrontal cortex to ensure coordinated goal-directed-behaviour [9].

In summary these results suggest that apathy is associated with other neurobehavioural syndromes, which are felt to involve dysfunction of frontosubcortical circuits.

Therefore the task force has attempted to formulate the criteria in such a way that they may be applied to disorders beyond those that constituted the focus of this work.

A second consideration concerns the assessment of apathy and present-day assessment instruments for practice and research. One of the main difficulties in the screening and assessment of apathy is that apathy in neuropsychiatric disorders is frequently associated with other phenomena. Instruments for the assessment of apathy in neuropsychiatric disorders (whether for screening or for estimating severity) must reliably distinguish apathy from other syndromes, particularly depression, which co-exist in these disorders. Ideally, the assessment should be structured, with input from the patient and the carer, and should also incorporate the physician's perspective. Furthermore, there is much validation work to be done and the task force is in the process of developing the relevant research, with the goal of producing estimates of the reliability and validity of present-day instruments (in relation to the diagnostic criteria). These data, when available, will facilitate the development of robust measures of severity and change, for treatment and other research. While we await the development of instruments that incorporate the criteria specified in this paper, the following instruments are recommended for practice and research; the Structured Clinical Interview for Apathy (SCIA)[44] which can be used for ascertainment of apathy in patients with dementia and other neurodegenerative diseases, the Apathy Evaluation Scale – AES [29], the Apathy Scale – AS [46], the Apathy Inventory – AI [42], the Lille Apathy Rating Scale – LARS [43]. The AES, AS, AI and LARS have the relevant psychometric properties for measuring the level of apathy.

6. Conclusion

Although diagnostic criteria for apathy have been proposed before and have also been used in research practice, they were proposed by individuals, and hence have no formal status, i.e., they are not part of international classification systems or endorsed by scientific societies. The present consensus criteria are the first that have been agreed upon within and between

scientific associations. The proposed criteria were endorsed by the participating associations, the French Association for Biological Psychiatry, the European Psychiatric Association, and the European Alzheimer Disease Consortium.

These present consensus diagnostic criteria for apathy were built on the work of others, and are proposed as a synthesis of current concepts, presented in semi-operationalized form, for practice and research application in the evaluation of various neuropsychiatric disorders. We suggest that, at least, these criteria have heuristic value since they attempt to solidify a somewhat loosely defined concept and thus make it more accessible and amenable to scientific study.

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References

[1] Aalten P, Verhey F, Boziki M, Bullock R, Byrne EJ, Camus V, et al. Neuropsychiatric syndromes in dementia; results from the European Alzheimer disease consortium. Dement Geriatr Cogn Disord 2007;24: 457–63.
[2] Aalten P, Verhey F, Boziki M, Bullock R, Byrne EJ, Camus V, et al. Consistency of neuropsychiatric syndromes across dementia; results from the European Alzheimer disease consortium. Dement Geriatr Cogn Disord 2008;25:1–8.
[3] Andreasen NC. The scale for the assessment of negative symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry 1989;7: 49–58.
[4] Benoit M, Koulibaly PM, Migneco O, Darcourt J, Pringuey DJ, Robert PH. Brain perfusion in Alzheimer's disease with and without apathy: a SPECT study with statistical parametric mapping analysis. Psychiatr Res Neuroimaging 2002;114(2):103–11.
[5] Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience. Brain Res Brain Rev 1998;28:309–69.
[6] Boyle PA, Malloy PF. Treating apathy in Alzheimer's disease. Dement Geriatr Cogn Disord 2004;17(1–2):91–9.
[7] Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 2001;30(2):619–39.
[8] Brown RG, Pluck G. Negative symptoms: the pathology of motivation and goal-directed behavior. Trends Neurosci 2000;23(9):412–7.
[9] Cohen JD, Botvinick MM, Carter CS. Anterior cingulate and prefrontal cortex: who's in control? Nat Neurosci 2000;3:421–3.
[10] Copeland MP, Daly E, Hines V, Mastromauro C, Zaitchik D, Gunther J, et al. Psychiatric symptomatology and prodromal Alzheimer's disease. Alzheimer Dis Assoc Disord 2003;17(1):1–8.
[11] Corbetta M, Miezin FM, Schulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci 1993;13:1202–26.
[12] Craig AH, Cummings JL, Fairbanks L, Itti L, Miller B, Li J, et al. Cerebral blood flow correlates of apathy in Alzheimer disease. Arch Neurol 1996;53:1116–20.
[13] Cummings JL, Mega MS, Gray K, Rosemberg-Thompson S, Gornbein T. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.
[14] Cummings JL, Mackell J, Kaufer D. Behavioral effects of current Alzheimer's disease treatments: a descriptive review. Alzheimers Dement 2008;4(1):49–60.
[15] Czanecki K, Kumar N, Josephs KA. Parkinsonism and tardive antecollis in frontotemporal dementia increased sensitivity to newer antipsychotics? Eur J Neurol 2008;15(2):199–201.
[16] Derouesné G. Apathy: a useful but limited concept. Psychol Neuropsychiatr Vieil 2004;2(1):19–28.
[17] Devinsky O, Morrell M, Vogt B. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279–306.
[18] Feldman H, Scheltens P, Scarpini E, Hermann N, Mesenbrink P, Mancione L, et al. Behavioral symptoms in mild cognitive impairment. Neurology 2004;62(7):1199–201.
[19] Frith CD. The cognitive neuropsychology of schizophrenia. 1 ed. Hove: L. Erlbaum Associates Publishers; 1992.
[20] Hermann N, Rothenburg LS, Black S, Ryan M, Liu BA, Busto UE, et al. Methylphenidate for the treatment of apathy in Alzheimer disease: prediction of response using dextroamphetamine. J Clin Psychopharmacol 2008;28(3):296–301.
[21] Holmes C, Wilkinson D, Dean C. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004;63:214–9.
[22] Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL. Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. Alzheimer Dis Assoc Disord 2004;18(1):17–21.
[23] Kuzis G, Sabe L, Tiberti C, Dorrego F, Starkstein SE. Neuropsychological correlates of apathy and depression in patients with dementia. Neurology 1999;52:1403–7.
[24] Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. J Am Geriatr Soc 2001;49:1700–7.
[25] Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, et al. Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998;10:314–9.
[26] Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2005:1–13 [published on line October 5].
[27] Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 2002; 288(12):1475–83.
[28] Marin RS. Differential diagnosis and classification of apathy. Am J Psychiatry 1990;147:22–30.
[29] Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res 1991;38:143–62.
[30] McPherson S, Fairbanks L, Tiken S, Cummings JL, Back-Madruga C. Apathy and executive function in Alzheimer's disease. J Int Neuropsychol Soc 2002;8(3):373–81.
[31] Mega MS, Cummings JL, Fiorello T. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–5.
[32] Migneco O, Benoît M, Koulibaly PM, Dygai I, Bertogliati C, Desvignes P, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and non demented patients. NeuroImage 2001;13:896–902.
[33] Mueser KT, McGurk SR. Schizophrenia. Lancet 2004;363(June 19): 2063–72.
[34] Onyike CU, Sheppard JM, Tschanz JT, Norton MC, Green RC, Steinberg M, et al. Epidemiology of apathy in older adults: the Cache County study. Am J Geriatr Psychiatry 2007;15(5):365–75.
[35] Padala PR, Burke WJ, Bhatia SC, Petty F. Treatment of apathy with methylphenidate. J Neuropsychiatry Clin Neurosci 2007;19(1):81–3.
[36] Politis AM, Vozzella S, Mayer LS, Onyike CU, Baker AS, Lyketsos CG. A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. Int J Geriatr Psychiatry 2004;19:1087–94.
[37] Ready RE, Ott BR, Grace J, Cahn-Weiner DA. Apathy and executive dysfunction in mild cognitive impairment and Alzheimer disease. Am J Geriatr Psychiatry 2003;11(2):222–8.
[38] Robert P, Berr C, Volteau M, Bertogliati C, Benoit M, Sarrazin M, et al. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one year follow up study. Clin Neurol Neurosurg 2006;108:733–6.

[39] Robert P, Verhey F, Byrne EJ, Hurt C, De Deyn PP, Nobili F, et al. Grouping for behavioral and psychological symptoms in dementia: clinical and biological aspects. Consensus paper of the European Alzheimer disease consortium. Eur Psychiatry 2005;20(7):490–6.

[41] Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Guerin O, et al. Importance of lack of interest in patients with mild cognitive impairment. Am J Geriatr Psychiatry 2008;16:770–6.

[42] Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry 2002;17:1099–105.

[43] Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's Disease. J Neurol Neurosurg Psychiatr 2006;77:579–84.

[44] Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. J Neurol Neurosurg Psychiatr 2005; 76:1070–4.

[45] Starkstein SE, Leentjens AFG. The nosological position of apathy. J Neurol Neurosurg Psychiatr 2008 [published online January 10].

[46] Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity and clinical correlates of apathy in Parkinsons's disease. J Neuropsychiatry Clin Neurosci 1992;4:134–9.

[47] Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. Am J Psychiatry 2001;158:872–7.

[48] Stuss DT, Van Reekum R, Murphy KJ. Differentiation of states and causes of apathy. 1 ed. New York: Oxford University Press; 2000.

[49] Van Reekum R, Stuss DT, Ostrander R. Apathy: why care? J Neuropsy Clin N 2005;17(1):7–19.

[50] Verghese J, Le Valley A, Derby C, Kuslansky G, Katz M, Hall C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. Neurology 2006;66(6):821–7.

[51] Vijayaraghavan L, Krishnamoorthy ES, Brown RG, Trimble MR. Abulia: a delphi survey of British neurologist and psychiatrist. Mov Disord 2002; 17(5):1052–7.

[52] Winograd-Gurvich C, Fitzgerald PB, Georgiou-Karistianis N, Bradshaw JL, White OB. Negative symptoms: a review of schizophrenia, melancholic depression and Parkinson's disease. Brain Res Bull 2006;70:312–21.

[53] Levy, Dubois. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cerb Cortex 2006;16(7):916–28.