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The prevalence, clinical correlates and treatment of apathy in Alzheimer's disease

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ABSTRACT – The aim for this article is to review the frequency, clinical correlates and treatment of apathy in Alzheimer's disease. Apathy is currently defined as diminished motivation as expressed in poor goal-oriented behaviours and cognitions. A structured clinical interview and a specific set of diagnostic criteria to diagnose apathy in dementia have been recently validated. There are several valid and reliable scales to measure the severity of apathy in adults with neuropsychiatric disorders. Apathy is present in about 20% of patients with mild dementia and in 60% of those with severe dementia. Among patients with Alzheimer's disease, apathy is significantly associated with older age, the presence of depression, and more severe cognitive and functional deficits, and also predicts a faster cognitive and functional decline. The mechanism of apathy in neuropsychiatric disorders is still unknown, but several studies suggest an important role for frontal lobe and basal ganglia dysfunction. There are no specific randomized controlled trials of psychoactive compounds to treat apathy in neuropsychiatric disorders. Evidence from case reports and small case series suggest the usefulness of psychostimulants to treat apathy in traumatic brain injury, whereas pharmacological trials for behavioural and psychological problems in dementia suggest that anticholinesterases may have some efficacy.

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Introduction

Diminished motivation is one of the most frequent behavioural changes among patients with neuropsychiatric disorders. Among patients with Alzheimer's disease (AD) the frequency of apathy has been reported to range from 25% to 50% (Burns *et al.* 1990, Starkstein *et al.* 1992, Starkstein *et al.* 1993, Starkstein *et al.* 1995, Levy *et al.* 1998). Apathy is most frequently associated with depression and severe dementia. AD patients with apathy are more impaired in basic activities of daily living and their caregivers report significantly higher levels of distress as compared to AD patients without apathy (Landes *et al.* 2001). In spite of the strong negative impact of apathy in AD, treatment studies for this frequent behavioural condition are surprisingly few.

Our group and others have also reported a relatively high frequency of apathy among patients with stroke lesions, traumatic brain injury, Parkinson's disease, and Huntington's disease (Burns *et al.* 1990, Starkstein *et al.* 1992, Starkstein *et al.* 1993, Starkstein *et al.* 1995, Levy *et al.* 1998). Nevertheless, the frequency of apathy is highest among individuals with dementia, and the present review will mainly focus on the frequency and clinical correlates of apathy in AD. We will briefly discuss the neurobiological basis of apathy, and also review pharmacological and non-pharmacological treatment modalities.

Diagnosis of Apathy

Marin defined apathy as the absence or lack of feeling, emotion, interest or motivation (Marin 1991). Marin and Wilkosz

(Marin & Wilkosz 2005) defined diminished motivation as the simultaneous decrease in goal-related aspects of overt behaviour, thought content and emotion in the presence of intact level of consciousness, attention, language, and sensorimotor capacity. Starkstein (Starkstein 2000) standardized Marin's construct into a set of criteria based on the presence of diminished goal-directed behaviour, diminished goal-directed cognition, and diminished concomitants of goal-directed behaviour (Table I). These diagnostic criteria have been validated for patients with Alzheimer's disease, but their validity in other neuropsychiatric conditions remains to be established.

One of the main diagnostic dilemmas is how to separate apathy from depression. Both the DSM-IV and the ICD-10 allow a diagnosis of depression in the absence of sad mood, provided the patient reports anhedonia and/or loss of interest. Marin (Marin *et al.* 1994) characterized "primary" apathy as consisting of the symptoms of apathy listed in Table I in the absence of the core symptoms of depression. Several studies from our group demonstrated that apathy is a common feature of depression among individuals with or without AD, although apathy and depression may also occur independently of each other (Starkstein *et al.* 2005).

Several instruments are now available to rate the severity of apathy. Marin and coworkers were the first to validate the *Apathy Evaluation Scale* for use with patients with stroke, Parkinson's disease, or Alzheimer's disease (Marin *et al.* 1994). This instrument consists of 18 items that can be administered as a self-rated scale, as a caregiver scale, or as a clinician administered test. Starkstein and coworkers developed a 14-item *Apathy Scale* (Table II), which is an abridged and slightly modified

version of Marin's instrument (Starkstein *et al.* 1995). The Apathy Scale was validated for use in stroke, Parkinson's disease, and Alzheimer's disease. Cummings developed the *Neuropsychiatric Inventory* as a multi-dimensional instrument administered to an informant (Cummings 1997). This assessment includes a specific module to measure apathy, which consists of 8 items that are rated as present or absent. Scores on the apathy module provide a measure of the frequency and severity of apathy, as well as caregiver distress. Roberts and coworkers designed the *Apathy Inventory* based on the format of the *Neuropsychiatric Inventory* (Robert *et al.* 2002). The Apathy Inventory also includes separate assessments for the symptoms of emotional blunting, lack of initiative, and loss of interest. More recently, Strauss & Sperry reported on the validity and reliability of the *Dementia Apathy Interview and Rating* to assess changes in motivation, emotional responsiveness and

engagement among patients with dementia (Strauss & Sperry 2002). We have recently published the validity and reliability of the *Structured Clinical Interview for Apathy* (Starkstein *et al.* 2005). This instrument includes questions assessing the domains of lack of motivation relative to the individual's previous level of functioning, lack of effort to perform every day activities, dependency on others to structure activities, lack of interest in learning new things or in new experiences, lack of concern about one's personal problems, unchanging or flat affect, and lack of emotional response to positive or negative personal events. Based on answers to specific questions, symptoms are scored as either absent, subclinical, or definitely present. This is, to our knowledge, the only standardized instrument to assess the presence of symptoms of apathy using a semi-structured format.

Table I
Diagnostic criteria for apathy (adapted from Marin (1991)).

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|----|---|
| A. | Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated either by subjective account or observation by others. |
| B. | Presence, while with lack of motivation, of at least 1 symptom belonging to each of the following three domains: |
| | <i>Diminished goal-directed behavior.</i> |
| | 1. Lack of effort. |
| | 2. Dependency on others to structure activity. |
| | <i>Diminished goal-directed cognition</i> |
| | 3. Lack of interest in learning new things, or in new experiences. |
| | 4. Lack of concern about one's personal problems. |
| | <i>Diminished concomitants of goal-directed behavior.</i> |
| | 5. Unchanging affect. |
| | 6. Lack of emotional responsivity to positive or negative events. |
| 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 (e.g., a drug of abuse, a medication). |
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Table II
Apathy Scale (Starkstein *et al.* 1995).

Questions	Not at all	Slightly	Some	A lot
1. Are you interested in learning new things?				
2. Does anything interest you?				
3. Are you concerned about your condition?				
4. Do you put much effort into things?				
5. Are you always looking for something to do?				
6. Do you have plans and goals for the future?				
7. Do you have motivation?				
8. Do you have the energy for daily activities?				
9. Does someone have to tell you what to do each day?				
10. Are you indifferent to things?				
11. Are you unconcerned with many things?				
12. Do you need a push to get started on things?				
13. Are you neither happy nor sad, just in between?				
14. Would you consider yourself apathetic?				

Note: For questions 1-8, the scoring system is the following: not at all = 3 points; slightly = 2 points; some = 1 point, a lot = 0 point.

For questions 9-14: the scoring system is the following: not at all = 0 points; slightly = 1 point; some = 2 points; a lot = 3 points.

In conclusion, whilst apathy is one of the most frequent behavioural changes in neuropsychiatric disorders, its clinical assessment is still problematic. Diagnostic criteria for apathy have been validated for Alzheimer's disease only. There is a variety of scales that are both valid and reliable to rate the severity of apathy, but these instruments are also used to diagnose apathy based on cut-off scores. This procedure may result in apathy groups with different syndromic clusters. There is also a structured clinical interview for apathy, but its validity and reliability has been established for patients with dementia only.

Frequency of apathy in Alzheimer's disease

We examined the frequency of apathy in a study that included a consecutive series of 101 patients with probable AD (Starkstein *et al.* 1995). Apathy was diagnosed based on ratings on the motivation and initiative item of the *Unified Parkinson's Disease Rating Scale* (Fahn & Elton 1987). Scores on this item are 0: normal, 1: less assertive than usual; more passive, 2: loss of initiative or disinterest in elective (non-routine) activities, 3: loss of initiative or disinterest in day to day (routine) activities, and 4: withdrawn,

complete loss of motivation. Patients with scores of 2 or higher were considered apathetic. Based on this diagnostic scheme, 46 of the 101 patients with Alzheimer's disease had apathy.

In the next study we diagnosed apathy based on the diagnostic criteria described in Table 1 (Starkstein *et al.* 2001). Clinical information was obtained from caregivers, who filled the Apathy Scale about the patient. Briefly, apathy was diagnosed whenever patients had 1) Poor or no motivation (as rated with item 7 on the Apathy Scale), 2) Poor or no interests (as rated with items 1 and 2) or effort (as rated with items 4 and 9), and 3) Feelings of indifference or lack of emotions most or all of the time (as rated with items 10 and 13). Based on this diagnostic scheme, apathy was diagnosed in 37% of a consecutive series of 319 patients with AD, as compared to none of a series of 36 age-comparable healthy individuals. About two thirds of the AD patients with apathy were also depressed (either major or minor depression).

In a recent study we assessed the Structured Clinical Interview for Apathy on a new series of 150 patients with AD. Apathy was diagnosed using the diagnostic criteria listed in Table I (Starkstein *et al.* 2005). We found that 19% of the patients met the diagnostic criteria for apathy. Thirteen of these 29 patients also had major depression, 5 patients had minor depression, and 11 patients were not depressed. Taken together, our findings suggest that the frequency of apathy in AD is lower when assessed with a structured interview and diagnosed with standardized criteria as compared to using arbitrary cut-off points on a severity rating scale.

In a study that included 131 patients with AD, Landes and coworkers diagnosed apa-

thy based on a cut-off score on the Dementia Apathy Interview and Rating (Landes *et al.* 2001). They diagnosed "frequent" apathy in 59% of the patients and found no significant association between higher levels of apathy and dysphoria. Using arbitrary cut-off scores on the Neuropsychiatric Inventory, the frequency of apathy was 27% in a population-based sample of 329 individuals with dementia (Lyketsos *et al.* 2000), 59% among 199 ambulatory patients living in the community (Aalten *et al.* 2003), 69% among 162 consecutive patients admitted to a dementia unit (Frisoni *et al.* 1999), and 76% among 435 patients with AD recruited from memory clinics (Mirakhur *et al.* 2004).

In conclusion, the frequency of apathy in AD has been reported to range from 19% to 76%, and several methodological issues may account for this wide discrepancy. First, apathy has been diagnosed using a variety of rating instruments and different strategies. Second, the source of patients varied widely, from patients living in the community to those admitted to specialized dementia units. Finally, those studies that included patients with relatively more severe dementia showed a higher frequency of apathy than studies that included patients with milder dementia.

Clinical correlates and course of apathy in AD

Most studies on apathy in AD have been cross-sectional, and all of them demonstrated a significant association between more severe apathy and more severe dementia. In a recent study we assessed the longitudinal evolution of apathy in a consecutive series of 354 patients with probable AD attending

a memory clinic (Starkstein *et al.* 2005). Apathy was assessed with the Apathy Scale and diagnosed using the diagnostic criteria shown in Table I. At baseline, apathy was diagnosed in 24% of the patients. Patients with apathy were significantly older, had more severe cognitive deficits and more severe impairments in activities of daily living than patients without apathy. The frequency of apathy ranged from 14% in very mild AD to 61% in the stage of severe AD. Whilst apathy was significantly associated with depression, the latter was neither necessary (apathy was present in 23% of patients without depression) nor sufficient to produce apathy (about half of the patients with depression did not meet the criteria for apathy).

A follow-up examination was carried out in 70% of the patients between one and four years after the baseline evaluation. To examine whether apathy should be considered a mere symptom of depression in dementia, we first examined whether the onset of depression during the follow-up period was associated with increasing apathy. This analysis included 97 patients with neither depression nor apathy at baseline, who had major ($N = 6$), minor ($N = 18$) or no depression ($N = 73$) at follow-up. The results showed a significant overall increment in apathy scores during the follow-up period, but there was no depression by apathy interaction (i.e., the increment in apathy scores was of similar magnitude for all patients, regardless of depression status at follow-up). These findings suggest that apathy in Alzheimer's disease should not be considered as a symptom of severe depression only.

We next examined whether apathy at baseline may predict more severe depression at follow-up. This study included non-depressed patients with ($N = 21$) or without

apathy ($N = 76$) at baseline. We found a significantly greater increase in depression scores during the follow-up period for patients with apathy as compared to those without apathy, suggesting that apathy is a significant predictor of depression in AD. Finally, we also found that patients with apathy at baseline or those that developed apathy during the follow-up period had a faster cognitive and functional decline than patients with no apathy at baseline or at follow-up. This replicates recent findings by Boyle and coworkers (Boyle & Malloy 2004) who found a significant correlation between apathy and more severe functional deficits.

In conclusion, apathy in Alzheimer's disease is associated with older age, more severe deficits in activities of daily living, and a faster progression of cognitive and functional impairments. In cross-sectional studies apathy was found to be significantly associated with depression, whereas in longitudinal studies apathy was found to be a significant predictor of more severe depression.

Mechanism of apathy in AD

The current view on the mechanism of apathy in neurological disorders is mostly mechanistic: apathy is considered to result from lesions in brain areas that mediate 'drive and motivation' and that participate in the elaboration of 'plans for actions'. In a recent review, Habib (2004) summarized the main clinical features of apathy (which he termed "athymormia") after brain damage, and stressed the over-representation of basal ganglia lesions among these patients. Recent studies emphasized the potential importance of parallel and segregated cortico-subcortical loops originating from and

terminating in the frontal lobes for the mechanism of neuropsychiatric disorders (Cummings 1993). One of these circuits originates in the anterior cingulate cortex, connects with the ventral globus pallidus and the dorsomedial thalamus, and projects back to the anterior cingulate. Habib speculated that this cingulate circuit may mediate “the process of converting motivation into action”, and that apathy may result from the bilateral disruption at different levels of this circuit or from lesions in limbic areas outside the striato-pallidal complex. This would explain why some patients with orbito-frontal lesions who mostly show disinhibited behaviours, also feature a concomitant loss of motivation. Habib concluded that “athymormia” is the result of a striatal-limbic disconnection syndrome characterized by deficits converting past or present emotional experience into action.

Habib’s proposal is certainly interesting and fits nicely with the current model of segregated basal ganglia-frontal lobe loops for the modulation of behaviour. However, Habib’s model partially rests on the dubious assumption that action is *causally* dependent on motivation. The problem with this hypothesis is how to avoid the Cartesian dilemma of psychological states (motivation and past or present emotional experiences) producing a physical state (action).

In a recent comprehensive review on the mechanism of apathy (termed the “auto-activation deficit”) Levy & Dubois emphasized that apathy should not be defined as “lack of motivation” (considered an obscure psychological concept), “but as an observable behavioural syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behaviours” (Levy & Dubois 2005). They further suggested that apathy may result from the disruption of

prefrontal cortex-basal ganglia circuits, considered to play a critical role in the generation and control of self-generated purposeful behaviour. Levy & Dubois considered that apathy may be related to the disruption of “emotional-affective”, “cognitive” and “auto-activation” processes. They hypothesized that disruption of an “emotional-affective” process may produce apathy due to the inability to associate affective and emotional signals with overt behaviour; disruption of the “cognitive” process may result from impairments on cognitive functions that are “needed to elaborate the plan of actions”; whereas the “auto-activation deficit” may result from “difficulties in activating thoughts or initiating the motor program necessary to complete the behaviour”.

It is not clear whether the behaviorist mechanism for apathy suggested by Levy & Dubois may successfully avoid the intrusion of psychological concepts into their model. They suggest that apathy may result from a faulty elaboration of “plans of action” and from the disruption of “activating thoughts” in the initiation of motor programs, which are both psychological concepts. Another limitation with Levy & Dubois model lies with the necessary linkage between apathy and lesions in specific brain areas. While most studies did demonstrate a significant association between apathy and lesions in the lateral prefrontal cortex and/or dorsal territories of the basal ganglia, these lesions are neither necessary (apathy may result from lesions elsewhere in the brain) nor sufficient to produce apathy (most patients with lesions in those brain areas do not develop apathy). Finally, whereas a strong association between apathy and cognitive impairments has been consistently demonstrated, it is uncertain

whether apathy may result from deficits restricted to executive functions.

In conclusion, current theories explain apathy as the behavioural expression of the disruption of cognitive modules that deal with the organization of human action, drive and motivation. These modules are considered to engage independent frontal-subcortical circuits. Future studies are needed to clarify the association between apathy and lesions in specific brain areas, as well as the role of executive dysfunction in the mechanism of apathy.

Treatment of apathy

There are few randomized controlled trials of pharmacological or non-pharmacological treatments for apathy in AD. On the other hand, there is a growing literature consisting of case reports and small series of patients that were treated for apathy with a variety of psychoactive agents (see Marin & Chakravorty for a comprehensive review (Marin & Chakravorty 2005)).

Politis and coworkers (Politis *et al.* 2004) carried out a randomized controlled trial to test the efficacy of a kit-based intervention to reduce apathy and increase quality of life in 37 patients with dementia. The control treatment consisted on one-to-one meetings with an activity therapist. The authors found a significant improvement on apathy measures over the course of the study, but there were no significant differences between the treatment groups on any of the outcome measures.

Lee and coworkers (Lee *et al.* 2003) have recently reviewed the pharmacological treatment of apathy among patients with traumatic Brain Psychostimulants and dopaminergic

agonists (e.g., methylphenidate, dextroamphetamine, pergolide and bromocriptine) may modestly improve arousal and speed of information processing, reduce distractibility, and improve some aspects of motivation and executive function (Plenger *et al.* 1996; Zafonte *et al.* 2001). However, the magnitude and temporal course of their therapeutic effect is still controversial (Whyte *et al.* 2002). A recent double blind, placebo controlled study evaluated the effects of methylphenidate on diverse cognitive functions in a group of 24 patients who had moderate to severe head injuries (Whyte *et al.* 2004). Methylphenidate, at 0.3 mg/kg/dose, showed clinically significant positive effects on speed of information processing, caregiver ratings of attention, as well as motivation and drive to complete other cognitive tasks (Whyte *et al.* 2004). However, another recent open study of 4 patients who developed apathy after a closed head injury suggests that selegiline has adequate efficacy to treat apathy and is better tolerated than methylphenidate, but these findings require confirmation in appropriate controlled trials (Newburn & Newburn 2005). Amantadine, a drug with complex pharmacologic effects on dopaminergic, cholinergic and NMDA receptors, could also have some efficacy to treat motivational deficits (Kraus & Maki 1997; Meythaler *et al.* 2002). Finally, there is some empirical evidence that cholinesterase inhibitors such as donepezil may improve cognitive functioning, motivation and general well being of patients with traumatic brain injury (Arciniegas *et al.* 1999, Freo *et al.* 2002, Arciniegas 2003).

In a study that included men with Parkinson's disease Ready and coworkers (Ready *et al.* 2004) found a significant correlation between low plasma levels of free testosterone and more severe apathy. The authors suggested that testosterone replacement

therapy may constitute a helpful treatment of apathy for these patients.

Several treatment studies suggested that anticholinesterase compounds may improve apathy among patients with dementia. In a recent study, Cummings and coworkers (Cummings *et al.* 2005) assessed the effect of rivastigmine to treat the neuropsychiatric disturbances of 173 nursing home residents with moderate to severe Alzheimer's disease. After 26 weeks of treatment there was a significant improvement of apathy, as measured with the Neuropsychiatric Inventory. It is important to stress that the effect of rivastigmine was not specific for apathy, since improvements were also noticed on other neuropsychiatric disturbances. Furthermore, changes on the Neuropsychiatric Inventory were rather small and may not have been clinically relevant. Thus, the beneficial effects of cholinergic therapy in AD needs to be replicated in larger, adequately powered clinical trials.

Conclusions

Apathy is being increasingly recognized as one of the most frequent behavioural changes among patients with neuropsychiatric disorders. Recent studies provided working definitions of apathy that were operationalized into standardized diagnostic criteria. A number of valid and reliable instruments have been developed to assess the severity of apathy. Apathy is highly prevalent among patients with dementia. Recent studies found that apathy in Alzheimer's disease is significantly associated with older age, relatively more severe cognitive deficits, depression, and more severe impairments in activities of daily living. Furthermore, patients with dementia

and apathy have a significantly faster cognitive and functional decline than demented individuals without apathy. The mechanism of apathy in neuropsychiatric disorders remains unknown, but recent studies suggest that disruption of frontal cortical-basal ganglia circuits and executive dysfunction may both play an important role. A variety of psychoactive compounds were reported to improve apathy after focal brain damage, but most of these studies consist of single cases or small case series. Anticholinesterase drugs may improve apathy in Alzheimer's disease, although this could be an epiphenomenon of improvement on other behavioural disorders. Important issues for further research are the validation of the clinical construct of apathy in neuropsychiatric disorders, better knowledge of those brain lesions that may be associated with apathy, and finding effective treatment modalities for this condition.

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