Chapter 14

Apathy as a Key Symptom in Behavior Disorders: Difference Between Alzheimer's Disease and Subcortical Vascular Dementia

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1. Introduction

There is currently no consensus on the nosological position of apathy in clinical practice. The clinical significance of negative symptoms such as apathy is increasingly recognized in neurological and psychiatric disorders, particularly those associated with frontal-subcortical dysfunction (Starkstein et al., 2008; Moretti et al., 2012). Apathy is defined as lack of motivation as manifested by diminished goal-directed behavior, reduced goal-directed cognition, and decreased emotional engagement, a reduced interest and participation in normal purposeful behavior, problems in initiation or sustaining an activity, lack of concern or indifference, and a flattening of affect. The prevalence of apathy in neurodegenerative disorders, such as Parkinson's disease vary between 16.5% and 51%, depending upon the instrument for assessment and on the samples examined. Apathy is quite common also in sVAD; different studies try to define its role in AD, but, even the most recent and well-conducted did not distinguish between early and advanced stages of AD, or even between AD and AD with parkinsonism (Starkstein et al., 2008; Stuss et al., 2000; Dujardin et al., 2009). It has been hypothesized that dysfunction of the nigro-striatal pathway may play an important role in the pathophysiology of apathy in neuro-degenerative disorders. In fact, apathy seems to be independent of disease duration, disability and severity of parkinsonism, and levodopa dose in PD, indicating that the brain changes underlying apathy differ from those associated with motor symptoms. Much more interesting is that not all the PD patients become apathetic, indicating that apathy should not entirely be considered a dopamine-dependent syndrome

in PD, and is in fact present even in not-purely dopaminergic alterations, such as AD or sVAD (Moretti et al., 2012; Levy et al., 1998; Brown and Pluck, 2000). Existing evidence suggests that apathy can be related to depression, as a key symptom of major depression or side-effect of antidepressant or antipsychotic drugs (Chase et al., 2011). Though, apathy and depression clearly dissociate in specific motor disorders, such as progressive supranuclear palsy, in which there is a high incidence of apathy but a low incidence of depression (Aarsland et al., 2001). Other Authors suggested that apathy might be a consequence of chronic disabling disease and its impact on mobility and opportunity for participation in normal activities. Thus, many Authors used the term "premature social aging" to describe the findings that patients with apathy have little in the way of interests or social activities, spending more time in solitary activities such as watching television or just sitting doing nothing (Starkstein et al., 1992). If apathy is a primary consequence of physical disability or impairment in daily living, then similar changes might be predicted for patients with articular/orthopedic impairment. Surprisingly, the osteoarthritis sample population, despite the motor disability, showed no evidence of apathy. It is thus likely that the physiopathology of apathy is a multifaceted entity. The aim of this preliminary was to assess the behavior spectrum of Alzheimer's Disease (AD) and that of subcortical Vascular Dementia (sVAD), with a particular concern for apathy, and to assess its possible role in the differential clinical diagnosis, as compared to other behavioral changes and different neuropsychological patterns.

We decided to conduct a prospective cohort study, designed to investigate behavioural alterations, and in particular apathy of an AD and of a sVAD population. Therefore, our group recruited 75 men and women aged 65–94 years, entering in Cognitive Disorder Unit Evaluation of the University of Trieste, with Mini-Mental State Examination (MMSE) scores of at least 14 and satisfying DSM-IV for dementia, and suffering from Alzheimer's Disease, according to NINDCS-ADRDA criteria (McKAhn et al., 1984) and 317 patients suffered from from subcortical vascular dementia, in accordance with the NINDS-AIREN criteria (Román et al., 1993); the patients have been selected from June 1st 2008 to June 1st 2011. In order to be enrolled into the study subjects had to show on brain MRI the classical pattern of atrophy of AD (hippocampal atrophy) and display hypoperfusion in temporoparietal and precuneus regions (AD) on HMPAO-SPECT. A patient was diagnosed as having subcortical VaD (sVaD) when the CT/MRI scan showed moderate to severe ischaemic white matter changes (Erkinjuntti et al., 1997) and at least one lacunar infarct. Brain CT-scans or MRI images were randomized and assessed independently, after the radiologist's opinion, by neurologists (RM, PT, RMA). The diagnosis was confirmed after 6 and 12 months of clinical follow-up.

Patients were not included in the study if they showed signs of normal pressure hydrocephalus, previous brain tumours, previous diagnosis of major stroke or brain haemorrhage. We did not include patients with white matter lesions, caused by specific aetiologies, such as multiple sclerosis, brain irradiation, collagen vascular disease, and genetic forms of vascular dementia (such as CADASIL or CARASIL). Patients with previous major psychiatric illness (i.e. schizophrenia, bipolar disorders, psychosis, compulsive-obsessive disorders, etc) or central nervous system disorders and alcoholism were excluded too. Exclusion criteria were, in addition to those provided by the corresponding diagnostic criteria, the absence of

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an informed caregiver, unavailability of neuroradiological examination, and/or the assumption of psychotropic drugs within two months prior to the clinical assessment. Therefore, five patients were excluded in consequence of lack of a sufficiently informed caregiver and twelve subjects were excluded because they assumed psychotropic drugs during the two months prior to our assessment.

Study subjects underwent a standardized baseline assessment that included a detailed history, a physical examination, laboratory tests and psychiatric evaluations. The physical examination included evaluations of pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel and carotid artery evaluation, electrocardiographic evaluation, and chest X-ray. All patients were followed with periodical neurological and neuropsychological examinations. A complete neuropsychological examination was conducted at baseline, and at 12 months' results were compared.

Main outcomes of the study were: Global performance, which was assessed using the Mini Mental State Examination (Folstein et al., 1975), Frontal Assessment Battery (FAB) (Dubois et al., 2000); Semantic and Phonological Fluency, Digit span subtest (digit span forward and backward) and arithmetic subtest (from Wechsler Adult Intelligent Scale-WAIS; Wechsler, 1981); global behavioral symptoms, assessed by the NeuroPsychiatric Inventory, NPI (Cummings et al., 1994); the caregiver stress, assessed by the Relative Stress Scale, RSS (Green et al., 1992). In addition to these main outcome measures, three further scales were used. The Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988); the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Greene et al., 1982), and the Clinical Insight Rating Scale (CIR) (Ott et al., 1986) (which provides a measure of its four comprising items – awareness, cognitive deficit, disease progression and functional deficit) were performed. In order to evaluate the apathy, as an independent scale (it is tested as specific item in NPI, and in BEHAVE-AD), we employed the Clinician/Researcher Rated Version of the Apathy Evaluation Scale (AES-C) (Marin et al., 1991). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0). Within Groups comparisons were performed by Wilcoxon Signed Rank tests. Between-group comparisons of changes were tested using the marginal homogeneity test, employing the Stewart Maxwell test. This was done for the overall scores for each efficacy variable. In addition, sub-analyses of Spearmann's rho correlation, 2-tailed analyses were performed between behavioral data obtained using the Apathy scores (AES-C), the FAB scores, Cornell's Depression Scores, RSS, CIR, and NPI scores. Results are presented as mean changes from baseline with standard deviations, and P-values are presented where appropriate.

The study subjects were 61 AD patients and 310 sVAD patients. All the patients could be fully studied (mean age 71.1 ± 7.3 years, range= 65-94 years). A synopsis of the cognitive performances obtained by the two groups has been reported in Table 1-2; a synoptic summary of the behavior scores has been reported in Table 3-4; the differential reappraisal of Apathy-scores (AES-C) has been reported in table 5-6. In summary, it can be stated that there are some important cognitive differences in the two groups: AD patients did worse in MMSE; they produced lower in phonological and semantic tasks, in arithmetic calculation and in digit tasks of WAIS; sVAD patients did generally worse in FAB tests. From the behavioral

perspective, the following aspects merged from the study: at baseline, the AD group had a worse score of NPI and BEHAVE-AD, and their caregivers did have a heavier stress, as stated by RSS. On the contrary, sVAD patients, at baseline did feel much more depressed (as stated by Cornell'Scale) and did have a better insight in their situation. After 12 months, AD patients showed higher NPI and Behave scores; sVAD patients did show more insight and remained more depressed. Surprisingly, the stress of the caregivers was not significantly different in the two groups. Very interestingly, sVAD patients did manifest more overt apathy, which merged from the AES-C scores, which increase during follow-up and remained a major key point in behavior disturbances of these patients. Spearman's rank correlation analyses indicated that there was a significant correlation between AES-C scores and RSS in sVAD ($r=0.88$, $p<0.01$); a negative correlation with FAB scores ($r=-0.81$, $p<0.01$); analyzing the sub-items, it can be stated a negative relationship between AES-S and C scores and the go/no-go strategies ($r=-0.71$, $p<0.05$); there was no relationship between apathy and depression and insight ratio.

baseline	sVAD	AD	P value (between group)
MMSE	25.8 (2.4)	22.1 (1.9)	<0.05
Word phonological fluency (WAIS)**	34.5 (7.9)	31.2 (3.6)	ns
Semantic category (WAIS)***	37.7 (5.6)	24.5 (3.2)	<0.01
Arithmetic calculations (WAIS) §	6.3 (1.6)	8.6 (1.2)	<0.05
Digit span forward (WAIS)	5.8 (1.5)	5.1 (0.6)	<0.05
Digit span backward (WAIS)	4.4 (2.5)	2.6 (0.8)	<0.05
FAB total score	11.2 (2.1)	10.8 (1.2)	ns
Analogies	2 (0.9)	1.6 (0.2)	ns
Phonemic fluency	1.6 (0.2)	1.8 (0.2)	ns
Motor series	2.2 (0.1)	2.7 (0.4)	ns
Contrast Instructions	2.3 (0.3)	2.2 (0.2)	ns
Go/no-go	0.8 (0.5)	0.9 (0.3)	ns
Comprehension	1.9 (0.1)	0.9 (0.2)	<0.05

Values are mean (SD). NS = not significant.. *Number of items in 45 seconds.; ** Total number of words produced, beginning with T, P, C;

*** Total number of words produced, comprised in the following categories: animal, fruits, professions ; § Number of mistakes

Table 1. Cognitive synoptical results obtained by the two groups studied

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12 months follow-up	sVAD within group (12 months vs baseline)	AD within group (12 months vs baseline)	P value (between group)
MMSE	23.8 (2.1) (-2 (.0.3); p<0.05)	17.1 (1.7) (-5 (0.2); p<0.01)	<0.01
Word phonological fluency (WAIS)**	29.5 (2.3) (-5 (5.6); p<0.01)	16.2 (3.1) (-15 (0.5); p<0.01)	<0.01
Semantic category (WAIS)***	27.1 (2.1) (-10.6 (3.5); p<0.01)	12.6 (1.3) (-9.9 (1.9); p<0.01)	<0.01
Arithmetic calculations (WAIS) §	5.4 (1.1) (-0.9 (0.5); ns)	3.4 (1.7) (-5.2 (0.5); p<0.01)	<0.05
Digit span forward (WAIS)	4.1 (1.4) (-1.7 (0.1); p<0.05)	3.2 (0.2) (-1.9 (0.4); p<0.05)	<0.05
Digit span backward (WAIS)	3.6 (0.3) (-0.8 (2.2); ns)	1.9 (0.1) (-0.5 (0.7); p<0.05)	<0.01
FAB total score	5.7 (1.5) (-5.5 (0.6); p<0.01)	7.5 (0.2) (-3.3 (1.0); p<0.05)	<0.01
Analogies	1.2 (0.1) (-0.8 (0.8); p<0.05)	1.4 (0.1) (-0.2 (0.2); ns)	ns
Phonemic fluency	(0.1) (-0.5 (0.1); p<0.05)	1.4 (0.1) (-0.4 (0.1); p<0.05)	ns
Motor series	1.1 (0.3) (-1.1 (0.5); p<0.01)	1.6 (0.2) (-0.9 (0.2); p<0.05)	ns
Contrast Instructions	1.2 (0.5) (-1.1 (0.3); p<0.01)	2.0 (0.1) (-0.2 (0.1); ns)	ns
Go/no-go	0.1 (0.3) (-0.7 (0.2); p<0.05)	0.8 (0.1) (-0.1 (0.2); ns)	ns
Comprehension	1.0 (0.9) (-0.9 (0.8); p<0.05)	0.3 (0.1) (-0.6 (0.1); p<0.05)	<0.05

Values are mean (SD). NS = not significant.. *Number of items in 45 seconds.; ** Total number of words produced, beginning with T, P, C;

*** Total number of words produced, comprised in the following categories: animal, fruits, professions ; § Number of mistakes

In brackets, in each column, comparison within group, 12 months vs baseline, reported as mean, SD, and p

Table 2. Cognitive synoptical results obtained by the two groups studied, at 12 months

baseline	sVAD	AD	P value
RSS	**24.7 (8.7)**	**36.1 (8.5)**	(p<0.01)
NPI	**14.9 (0.3)**	**24.4 (5.2)**	(p<0.01)
CIR	**3 (0.2)**	**2 (0.5)**	(p<0.05)
Cornell	**18.5 (3.5)**	**13.5 (4)**	(p<0.05)
BEHAVE	**9.5 (2.1)**	**12.6 (4.1)**	(p<0.05)

Values are mean (SD). NS = not significant..

Table 3. Behavioral synoptical results

	sVAD	AD	P value
RSS	44.5 (1.6) (+20.2 (5.9), <0.01)	43.9 (2.1) (+7.8 (6.8), <0.05)	ns
NPI	24.1 (0.8) (+10.8 (0.5), <0.01)	56.3 (4.5) (+31.9 (1.1), <0.01)	(p<0.01)
CIR	2.7 (0.3) (+0.3 (0.1), ns)	(0.3) (+1.0 (0.3), <0.05)	(p<0.01)
Cornell	22.1 (1.2) (+4.4 (2.3), <0.05)	12.3 (1.1) (-0.8 (3.1), ns)	(p<0.01)
BEHAVE	22.7 (1.3) (+13.2 (0.8), <0.01)	43.1 (2.3) (+30.5 (0.8), <0.01)	(p<0.01)

Values are mean (SD). NS = not significant.; In brackets, in each column, comparison within group, 12 months vs baseline, reported as mean, SD, and p

Table 4. Behavioral synoptical results

baseline	sVAD	AD	P value
AES-C	48.5 (7.2)	28.0 (4.9)	<0.01

Values are mean (SD). NS = not significant.

Table 5. Apathy scores, by the researcher evaluation (AES-C)

	sVAD	AD	P value
AES-C	67.2 (3.5) (+18.7 (3.7); p<0.01)	33.4 (6.1) (5.4 (1.2); ns)	<0.01

Apathy scores, by the researcher evaluation (AES-C)

Table 6. Values are mean (SD). NS = not significant.. In brackets, in each column, comparison within group, 12 months vs baseline, reported as mean, SD, and p

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What merged from this study is a confirmation of the wide known rule, that behavioral disorders are the most problematic in the follow-up of dementia. Among them, apathy is one of the most concerning. Frequency and severity of apathy vary across different dementia subtypes; it is the most common behavioral symptom of behavioral variant of frontotemporal dementia (bvFTD), with reported prevalence ranging from 62 to 89% of patients (Mendez et al., 2008); the prevalence of apathy in AD ranges from 25 to 88% with a trend to increase with disease severity (Starkestein et al., 2006). The prevalence of apathy in other neuro-degenerative disorders, such as Parkinson's disease vary between 16.5% and 51%, depending upon the instrument for assessment and on the samples examined (Moretti et al., 2012). Apathy may be associated with an increased risk of cognitive decline. Symptoms of apathy, but not symptoms of depressive affect, increase the risk of progression from MCI to AD (Richard et al., 2012). Conversely, patients with or without apathy had an increase of similar magnitude in anosognosia scores. In conclusion, anosognosia is a significant predictor of apathy in Alzheimer's disease (Starkstein et al., 2010).

The aim of our study was to assess the behavior spectrum of Alzheimer's Disease (AD) and that of subcortical Vascular Dementia (sVAD), with a particular concern for apathy, and to assess the possible role of apathy in the differential clinical diagnosis, as compared to other behavioral changes and different neuropsychological patterns. Our results showed that there are some important cognitive differences in the two groups. Obviously, the AD patients did worse in MMSE; they produced lower in phonological and semantic tasks, they did many mistakes in arithmetic calculation and their digit span were lower; sVAD patients did generally worse in FAB tests, as a sensitive measure of executive dysfunction. And their behavior problems were different. At baseline, the AD group had a worse score of NPI and BEHAVE-AD, and their caregivers did have a heavier stress, as stated by RSS. On the contrary, sVAD patients, at baseline did feel much more depressed (as stated by Cornell'Scale) and did have a better insight in their situation. After 12 months, AD patients showed higher NPI and Behave scores; sVAD patients did show more insight and remained more depressed. Surprisingly, the stress of the caregivers was not significantly different in the two groups. Very interestingly, sVAD patients did manifest more overt apathy, which merged from the AES-C scores, which increased during follow-up.

So far, it can be argued that sVAD patients have higher insight, more depression and more apathy than AD, and the two last aspects are the major causative factors for an increase of caregiver stress in the one-year follow-up. At that time, the significant difference which was noted at the beginning of the study for the RSS of AD patients, is practically cancelled out, and there is no difference between RSS in AD and sVAD patients. The main reason for what observed is that apathy increases, and caregivers do not know how to manage it. Apathy is one of the greatest stressors for caregivers, and the second most common is disinhibition (Massimo et al., 2009).

As a general observation (Quaranta et al., 2012), the occurrence of apathy is connected to damage of prefrontal cortex (PFC) and basal ganglia (Chase, 2011); "emotional affective" apathy may be related to the orbitomedial PFC and ventral striatum; "cognitive apathy" may be associated with dysfunction of lateral PFC and dorsal caudate nuclei; deficit of "autoactivation" may

be due to bilateral lesions of the internal portion of globus pallidus, bilateral paramedian thalamic lesions, or the dorsomedial portion of PFC (Chow et al. 2009). Trying to compare apathy in AD and in the behavior form of Frontal dementia (bvFTD), Quaranta et al (2012) lead to an observation of a different distribution of apathetic symptoms; they stated that subjects affected by bvFTD displayed higher frequency of "affective" symptoms, and a reduction of "auto-activation" (Levy and Dubois, 2006) (or "behavioral apathy," (Marin, 1991)) in comparison with AD sample. The different clinical expression of apathy, among the two groups of patients probably reflects the involvement of different anatomic substrates. Previous studies have reported that in bvFTD apathy is associated with changes in orbitofrontal cortex (Zamboni et al., 2008; Peters et al., 2006), which, in turn, has been postulated to be the anatomical correlate of "affective" apathy (Levy and Dubois, 2006), and with volume loss in the dorsal anterior cingulate and dorsolateral prefrontal cortex (Massimo et al., 2009). Thus, it is possible that the observation by Quaranta et al (2012) may reflect an alteration of orbitofrontal cortex and its connections with subcortical nuclei (ventral striatum), that could be specific of bvFTD. "Affective apathy" may be also regarded as the clinical expression of personality changes in bvFTD; for example, Sollberger et al. (2009) reported that subjects with FTD and semantic dementia displayed a reduction in affiliative behavior (lack of warmth) and showed, in a large sample of subjects aff ected by different neurodegenerative diseases, an association between "warmth" and several cortical and subcortical right hemisphere structures (viz. orbitofrontal cortex, insular cortex, amygdala, and hippocampal and parahippocampal regions). This finding is of particular interest, since the authors reported an association between lack of warmth and cerebral structures related to reward mechanisms, and "affective apathy" has been regarded as consequence of the inability to associate emotions to behaviors (Marin, 1991; 1996). Analogously, affective apathy may be related to an impairment of the so-called prosocial sentiments (such as guilt, pity, and embarrassment), connected to lack of empathy; Moll et al. (2011) reported reduced social sentiments in bvFTD subjects; this deficit was related to hypometabolism in medial frontal polar cortex and septal area.

On the other hand, in AD, apathy severity has been connected to neurofibrillary tangles density in the anterior cingulate gyrus (Marshall et al., 2006) and to grey matter atrophy in the anterior cingulate and in the left medial frontal cortex (Apostolova et al, 2007; Tekin et al., 2001; Marshall et al., 2006). These findings were confirmed by a PET study showing the association of apathy with hypometabolism in the bilateral anterior cingulate gyrus and medial orbitofrontal cortex (Marshall et al., 2007). Many studies tried to identify the neuroanatomical correlates of apathy in AD (Tunnard et al., 2011). Functional imaging studies have tended to find impaired functioning measured by either reduced blood flow or reduced metabolism in the anterior cingulate cortex (ACC) and medial frontal or orbitofrontal cortical (OFC) brain regions (Robert et al., 2006; Lanctot et al., 2007; Marshall et al., 2007). However, it is uncertain whether these regions are unilaterally or bilaterally affected. Others have found reduced function limited to the OFC alone (Holthoff et al., 2005) or the ACC alone (Migneco et al., 2001), suggesting that impaired functioning of both regions is not necessary for apathy to result. MRI studies investigating the structural correlates of apathy in AD patients have, for the most part, replicated findings from functional studies implicating the ACC and OFC most consistently (Apostolova et al., 2007;Laveretsky et al., 2007; Bruen et al., 2008). Additional regions of atrophy in the superior frontal gyrus, specifically BA 9, are also

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reported (Apostolova et al., 2007; Bruen et al., 2008) as is atrophy of frontopolar (BA 10) and ventrolateral prefrontal regions, including BA 45 (pars triangularis; Bruen et al., 2008).

Also of note, is some evidence that subcortical nuclei which project to prefrontal regions, including the caudate and putamen have shown greater atrophy in apathy in AD (Bruen et al., 2008). Overall then, functional, structural and pathological studies point towards a specific involvement of the ACC and OFC in mediating symptoms of apathy, with a suggestion of wider involvement of frontocortical networks.

One pathophysiological model for apathy in Alzheimer's disease which addresses both structural and biochemical disruption is that of Guimaraes et al. (2008). Their model proposes that the ACC and OFC are part of a broader fronto striatal circuit, which is involved in decision-making. Specifically, these regions are involved in evaluating action and outcomes and, via the basolateral amygdala and nucleus accumbens, feed into an ascending frontostriatal pathway to the dorsolateral prefrontal cortex, which is ultimately responsible for selecting and executing behavioural responses. Damage to the ACC and OFC leads to a disruption of this circuit resulting in impaired decision-making and impaired response initiation, which presents as apathy.

This model resembles quite well our idea of apathy in sVAD. There is good evidence of high levels of apathy subcortical disease, such as Parkinson's Disease, resulting from dysfunction at the striatal level (Pluck and Brown, 2002), and our data suggest than in AD the locus of dysfunction is at the cortical level, namely the ACC and the OFC.

In sVAD, apathy might be the result of a wider prefrontal disease process, or may suggest a putative role for these regions in mediating apathy, namely due to an involvement of the pars triangularis, of the superior frontal gyrus and of the orbital operculum may suggest that degeneration of the OFC is part of. Ventrolateral and superior frontal regions are also involved in the selection and execution of willed action, and so may contribute to the diminished behavioural responses to everyday challenges displayed by apathetic patients. Recently, increased incidence of white matter hyperintensities in the frontal lobe has been associated with apathy (Starkstein et al., 2009); however, some studies have found no evidence of frontal involvement in apathy (Rosen et al., 2005). A recent and well conducted study examined the relationship between behavior alterations and subcortical lesions (white-matter lesions and lacunes) in AD (Palmqvist et al., 2011). Lacunes in the basal ganglia resulted in a 2- to 3-fold increased risk of delusions, hallucinations and depression, when adjusting for cognition and atrophy. This suggests that basal ganglia lesions can contribute to BPSD in patients with AD, independently of the AD process (Palmqvist et al., 2011).

Being that we have chosen sVAD and AD patients, we have tried to avoid the spurious cases of AD/sVAD coexistence. What we have found is a major involvement of subcortical frontal circuits in sVAD, than in AD, and deriving from that, major evidence of apathy in sVAD, than in AD. In normal conditions, one may propose that the prefrontal cortex internalizes the information from the external and internal environments needed to make a decision about possible actions to be elaborated and performed. Neural signals corresponding to the thoughts or actions are then processed by the basal ganglia in order to validate the most relevant signal. Validation processing may be translated into the extraction of the relevant signal from noise to be read-

dressed to the output target, namely the prefrontal cortex (Levy and Dubois, 2006), where a clear-cut signal can be detected and contributes to disambiguating decision-making and maintaining or modifying the ongoing behaviour. In pathological situations, if there is a focal destruction within the basal ganglia sub-regions, the signal emerging from the basal ganglia is diminished, the ongoing behaviour is not validated (i.e. not amplified) at the level of the cortex and could be difficult to maintain, and the forthcoming one (if it is not reflexive) is not activated (Levy and Dubois, 2006). In sum, an 'auto-activation' deficit results from the inability of voluntary thoughts or actions to reach the activation threshold due to a decreased signal-to-noise ratio at the level of the prefrontal cortex (Levy and Dubois, 2006).

Thus, in that way, we can justify apathy in sVAD due to the major involvement of cortical-subcortical neural pathways. Many studies should be done to differentiate the anatomical, biological, and physiological eventual different substrate in the subcortical vascular forms, and in degenerative disorders, in order to better differentiate them, if necessary, and eventually to treat them.

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References

[1] Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2001;13:42–9.

http://dx.doi.org/10.5772/54264

[2] Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biol Psychiatry 1988; 23: 271–84.

[3] American Psychiatric Association. DSM-IV (4th ed.) 1994; Washington, DC: American Psychiatric Association.

[4] Brown RG, Pluck G. Negative symptoms: the "pathology" of motivation and goal-directed behaviour. Trends Neurosci 2000;23:412–17.

[5] Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308–14.

[6] Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000 Dec 12;55(11):1621-6.

[7] Dujardin K, Sockeel P, elliaux M, DESTEE A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinsons's Disease. Movement Disorders, 2009 (24); 16: 2391-2397.

[8] Erkinjuntti T. Vascular dementia: challenge of clinical diagnosis. Int Psychogeriatr 1997;9: 77–83.

[9] Folstein M, Folstein S, McHugh P. Mini-Mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[10] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," Neurology, 1984; 34, 7. 939–944.

[11] Greene JG, Smith R, Gardiner M, Timburg GC. Measuring behavioural disturbance of elderly demented in patients in the community and its effects on relatives: a factor analytic study. Age Ageing 1982; 11: 121–6.

[12] Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998;10: 314–19.

[13] Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatr Res 1991; 38:143–62.

[14] Moretti R, Torre P., Antonello RM, Vidus rosin M, Esposito F, Rubelli Furman M, Bellini G. Apathy: a complex symptom, specific to the clinical pattern pf presentation of Parkinson's Disease. Am. J .Alzheimer's Disease and other Dementias, 2012; Volume 27 (3) 2012 pp. 196 - 201.

[15] Ott BR, Lafleche G, Whelihan WM, et al. Impaired awareness of deficits in Alzheimer's Disease. Alzheimer Dis Assoc Disord 1996; 10: 68–76.

[16] Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatr 1987; 48(S1): 9–15.

[17] Roman GC, et al. Vascular dementia: Diagnostic criteria for research studies. (Report of the NINDS-AIREN Intemational Workshop) Neurology,1993; 43, 250-260.

[18] Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatr 2008; 10; 202-209.

[19] Starkstein SE, Mayberg SE, Preziosi TJ, et al. Reliability, validity and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry 1992;4:134–9.

[20] Stuss DT, Van Reekum R, Murphy KJ. Differentiation of states and causes of apathy. In: Borod JC(ed.): The Neuropsychology of emotion. Oxford: Oxford University Press. 2000. Pp. 340--363.

[21] Chase T. N. "Apathy in neuropsychiatric disease: diagnosis, pathophysiology, and treatment," Neurotoxicity Research, 2011; vol. 19, no. 2: pp. 266–278.

[22] Wechsler D. Wechsler adult intelligence scale manual-R. New York: Grune & Stratton. 1981.

[23] Mendez M. F., Lauterbach E. C., Sampson S. M. An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research Journal of Neuropsychiatry and Clinical Neurosciences, 2008; vol. 20, no. 2: 130–149

[24] Starkstein S. E., Jorge R., Mizrahi R., Robinson R. G. A prospective longitudinal study of apathy in Alzheimer's Disease Journal of Neurology, Neurosurgery & Psychiatry, 2006; vol. 77, no. 1: 8–11.

[25] Chow T. W., Binns M. A., Cummings J. L. et al. Apathy symptom profile and behavioral associations in frontotemporal dementia vs dementia of Alzheimer type," Archives of Neurology, 2009; vol. 66, no. 7: 888–893.

[26] Zamboni G., Huey E.D., Krueger F., Nichelli P. F., Grafman J. Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates, Neurology, 2008; vol. 71, no. 10: 736–742.

[27] Peters F., Perani D., Herholz K. et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal Dementia. Dementia and Geriatric Cognitive Disorders, 2006; vol. 21, no. 5-6: 373–379.

[28] Massimo L., Powers C., Moore P. et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dementia and Geriatric Cognitive Disorders, 2009; vol. 27, no. 1: 96–104.

[29] Marshall G. A., Fairbanks L. A., Tekin S., Vinters H. V., Cummings J. L. Neuropathologic correlates of apathy in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 2006; vol. 21, no. 3: 144–147.

[30] Apostolova L.G., Akopyan G. G., Partiali N. et al. Structural correlates of apathy in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 2007; vol. 24, no. 2: 91–97.

http://dx.doi.org/10.5772/54264

[31] Marshall G. A., Monserratt L., Harwood D., Mandelkern M., Cummings J. L., Sultzer D. L. Positron emission tomography metabolic correlates of apathy in Alzheimer disease. Archives of Neurology, 2007; vol. 64, no. 7: 1015–1020.

[32] Marin R. S. Apathy: a neuropsychiatric syndrome. Journal of Neuropsychiatry and Clinical Neurosciences, 1991; vol. 3, no. 3: pp. 243–254.

[33] Marin R. S. Apathy: Concept, Syndrome, Neural Mechanisms, and Treatment," Seminars in Clinical Neuropsychiatry, 1996; vol. 1, no. 4: 304–314.

[34] Moll J., Zahn R., de Oliveira-Souza R. et al. Impairment of prosocial sentiments is associated with frontopolar and septal damage in frontotemporal dementia," NeuroImage, 2011; vol. 54, no. 2: 1735–1742.

[35] Quaranta D, Marra C, Rossi C, Gainotti G, Masullo C. Different Apathy Profile in Behavioral Variant of Frontotemporal Dementia and Alzheimer's Disease: A Preliminary Investigation. Current Gerontology and Geriatrics Research, 2012; Article ID 719250, 8 pages; doi:10.1155/2012/719250

[36] Tunnard C., Whitehead D., Hurt C., Wahlund L.O., Mecocci P., Tsolaki M., Vellas B., Spenger C., Kłoszewska I., Soininen H., Lovestone S., Simmons A., on behalf of the AddNeuroMed Consortium. Apathy and cortical atrophy in Alzheimer's disease. Int J Geriatr Psychiatry 2011; 26: 741–748.

[37] Apostolova LG, Akopyan GG, Partiali N, et al. Structural correlates of apathy in Alzheimer's disease. Dement Geriartr Cogn Disord. 2007; 24: 91–97.

[38] Bruen PD, McGeown WJ, Shanks MF, Vennner A. Neuroanatomical correlates of neuropsychiatric sypmptoms in Alzheimer's disease. Brain 2008; 131: 2455–2463.

[39] Guimara˜es HC, Levy R, Teixeira AL, Beato RG, Caramelli P. Neurobiology of apathy in Alzheimer's disease. Arq Neuro-Psiquiatr. 2008; 66: 436–443.

[40] Holthoff VA, Beuthien-Bauman B, Kalbe E, et al. Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. Biol. Psychiatry 2005; 57: 412–421.

[41] Lanctot KL, Moosa S, Herrmann N, et al. A SPECT study of apathy in Alzheimer's disease. Dement Geriartr Cogn Disord. 2007; 24: 65–72.

[42] Laveretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. Am J Geriatr Psychiatry 2007; 15: 386–394.

[43] Marshall GA, Fairbanks LA, Tekin S, Vinters HV, Cummings JL. Neuropathologic correlates of apathy in Alzheimer's disease. Dement Geriatr Cogn Disord. 2006; 21: 144–147.

[44] Marshall GA, Monserratt L, Harwood D, et al. Positron emission tomography metabolic correlates of apathy in Alzheimer's disease. Arch Neurol. 2007; 64: 1015–1020.

[45] Migneco O, BenoitM, Koulibaly PM, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and nondemented patients. Neuroimage 2001; 13: 896–902.

[46] Pluck GC, Brown RG. Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatr 2002; 73: 636–642.

[47] Robert PH, Darcourt G, Koulibaly MP, et al. Lack of initiative and interest in Alzheimer's disease: a single photon emission computed tomography study. Eur J Neurol 2006; 13: 729–735.

[48] Rosen HJ, Allison SC, Schaeur GF, et al. Neuroanatomical correlates of behavioral disorders in dementia. Brain 2005; 128: 2612–2625.

[49] Starkstein SE, Mizrahi R, Capizzano AA, et al. Neuroimaging correlates of apathy and depression in Alzheimer's Disease. J Neuropsychiatry Clin Neurosci. 2009; 21: 259–265.

[50] Tekin S, Mega MS, Masterman DM, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer's disease. Ann Neurol 2001; 49: 355–361.

[51] Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndrome validity of apathy in Alzheimer's disease. Am. J. Psychiatry 2001; 158: 872–577.

[52] Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. J. Affect. Disord. 1993; 28: 7–14.

[53] Clarke DE, Van Reekum R, Patel J, Simard M, Gomez E, Streiner DL. An appraisal of the psychometric properties of the clinician version of the Apathy Evaluation Scale (AESC)- Int. J. Methods Psychiatr. Res. 2007; 16: 97–110.Resnick B, Zimmerman SI, Magaziner J et al. Use of the Apathy Evaluation Scale as a measure of motivation in elderly people. Rehabil. Nurs. 1998; 23: 141–147.

[54] Tatsch M, Bottino CM, Azevedo D et al. Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, non-demented elderly from a community-based sample in Brazil: Prevalence and relationship with dementia severity. Am. J. Geriatr. Psychiatry 2006; 14: 438–445.

[55] Jung Hsieh C, Chu H, Jror-Serk Cheng J, Shen WW, Lin CC. Validation of apathy evaluation scale and assessment of severity of apathy in Alzheimer's disease.pcn_Psychiatry and Clinical Neurosciences 2012; 66: 227–234

[56] Starkstein SE, Brockman S, Bruce D, Petracca G. Anosognosia Is a Significant Predictor ofApathy in Alzheimer's Disease. The Journal of Neuropsychiatry and Clinical Neurosciences 2010; 22:378 –383

[57] Richard E, Schmand B, Eikelenboom P, Yang SC, Ligthart SA, Moll van Charante EP, van Gool WA. Symptoms of apathy are associated with progression from mild cogni-

http://dx.doi.org/10.5772/54264

tive impairment to Alzheimer's disease in non-depressed subjects. Dement Geriatr Cogn Disord. 2012;33(2-3):204-9.

[58] Palmqvist S, Sarwari A, Wattmo C, Bronge L, Zhang Y, Wahlund LO, Nägga K. Association between subcortical lesions and behavioral and psychological symptoms in patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 2011;32(6):417-23.

[59] Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, Libon DJ, Grossman M. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord. 2009;27(1):96-104.

[60] Levy R., Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cerebral Cortex, 2006; 16, 7: 916–928.

[61] Moretti R, Torre P, Antonello RM (Eds). Basal Ganglia and Thalamus: their role in cognition and behavior. Novascience Editor, NewYork. 2009.

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