NEUROBIOLOGY OF APATHY IN ALZHEIMER’S DISEASE

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Abstract – Apathy is considered the most frequent neuropsychiatric disturbance in dementia and its outcome is generally deleterious. Apathy can be related to a dysfunction of the anatomical-system that supports the generation of voluntary actions, namely the prefrontal cortex and/or the prefrontal-subcortical circuits. In Alzheimer’s disease, pathological and neuroimaging data indicate that apathy is likely due to a dysfunction of the medial prefrontal cortex. Accordingly, in this review article, we propose a pathophysiological model to explain apathetic behavior in Alzheimer’s disease, combining data from neuroimaging, neuropathology and experimental research on the role of orbito-frontal cortex, anterior cingulate cortex, basal ganglia and dopamine in decision-making neurobiology.

KEY WORDS: apathy, Alzheimer’s disease, decision-making, orbito-frontal cortex, anterior cingulate cortex, basal ganglia, dopamine.

Apathy definition, epidemiology, diagnosis and clinical implications

Marin defined apathy as “a lack of motivation not attributable to diminished level of conscience, cognitive impairment or emotional distress”¹³. Recently, Levy and Du
bois proposed a phenomenological approach to define apathy, considering it as a "quantitative reduction of self-generated voluntary and purposeful behaviors". According to this contemporary view, apathy may be caused by dysfunction of any steps necessary to achieve goal-directed behavior as follows: internal and external determinants that motivate behavior, selection of goals, elaboration of a plan of action, initiation, execution, evaluation of goals achieved and feedback control of the behavior response. Hence, it is hardly surprising that this complex set of processes may be compromised in demented patients, especially in advanced stages of disease.

Apathy has been shown to be the most common behavioral change in AD. Its prevalence depends on the type of population studied, the diagnostic criteria and the type or severity of dementia. When diagnosed with the Neuropsychiatric Inventory (NPI) in outpatient settings, apathy prevalence ranged from 55% to 80%, and from 36% to 53% in community based samples of AD patients. van Reekum and coworkers' pooled analysis found a point prevalence of 60.3% in outpatients with AD.

Apathy is somewhat difficult to isolate from depression: apathy is often a symptom observed in depression. However, apathy can occur without depression in AD and when depression and apathy co-occur in AD patients, it has been shown that they are clinically and anatomically independent. Indeed, in order to discriminate apathy from depression, several scales have been designed to quantify apathy, which wisely exclude symptoms such as sadness and negative thoughts, typically observed in depressive syndromes.

There is now a large body of clinical evidence that apathy has construct validity with particular phenomenological, prognostic and therapeutic features.

1. The typical apathetic patient usually lacks the negative thoughts, sadness and somatic complaints frequently observed in mood disorders. Furthermore, apathy has been associated with extrapyramidal signs and neuropsychological deficits which cannot be explained by depressive symptoms.

2. Apathetic symptoms are predictors of worse clinical outcomes in prospective studies: MCI patients with high apathy scores have increased risk of dementia at follow-up; apathetic AD patients have faster functional and cognitive decline. Additionally, apathy seems to be more prevalent as dementia progresses and is also a relatively permanent behavior once following onset, in contrast to depression whose prevalence appears to be reduced in advanced stages. Furthermore, factor analysis of neuropsychiatric symptoms in dementia has repeatedly shown a division of depression and apathy into separate behavioral dimensions.

3. Response to treatment is also different: anti-depressants, especially selective serotonin reuptake inhibitors (SSRI), seem to have no therapeutic benefit in apathetic patients or can even increase the severity of apathy. Indeed, it has recently been shown that elderly depressed patients on SSRI had elevated apathy scores despite similar improvement in depressive symptoms when compared to the group treated with other anti-depressants. Alternatively, Padala and coworkers documented a dissociation between apathetic symptom improvement and absence of global depression score change in a depressed patient treated with methylphenidate.

Prefrontal cortex-basal ganglia circuits and generation of voluntary actions

The basal ganglia and their connections with prefrontal cortex (PFC) are essential to decision-making. Hence, it is not surprising that fronto-striatal circuit dysfunction may be responsible for the emergence of apathetic behavior in a wide range of neurological disorders. According to Levy and Dubois, apathy must be understood as a heterogeneous disorder, resulting from at least three different phenomena related to distinct basal ganglia topography. The first, ascribed to affective-emotional processing, involves the ventromedial PFC and its connection with the ventral striatum and amygdala. This circuit integrates the affective or emotional value of a given stimulus into the ongoing behavior. The second, ascribed to cognitive processing, involves the lateral PFC and the dorsal caudate nucleus. Essentially, this circuit is responsible for the executive elaboration of the plan of actions responsible for goal-directed behavior. The third, "auto-activation" processing, is observed in the most severe forms of apathy, characterized by difficulties in self-initiating actions or thoughts, contrasting with relatively spared, externally driven response. This pattern, called the "auto-activation deficit" may be observed after bilateral lesions in the internal portions of the pallidum, or after extensive damage to the medial wall of the PFC. The latter topography of lesion, however, may not represent a good framework to understand apathy in as far as its great extension makes it difficult to draw specific functional conclusions.

The basal ganglia combine spatial segregation, because of its multiple parallel circuits connecting different PFC regions, and signal convergence, displaying progressive concentration of fibers from cortex into the pallidum. This structural arrangement makes these structures a suitable place to extract a relevant signal from background noise arising from multiple input (parallel loops), and to amplify it throughout its final pathway. The resulting selection is
then transferred back to the PFC, generating relevant neural signals in output targets such as cognitive and limbic territories, especially the medial PFC. Thus, the unequivocal importance of basal ganglia in the generation of behavior output should be taken in conjunction with clinical, pathological and neuroimaging findings from AD patients in any attempt to understand apathy in this type of dementia.

Evidence from mild cognitive impairment (MCI) patients and pre-dementia depressive syndromes point to the clinical relevance of apathetic behavior, even in early stages of cognitive decline\(^6\). The neuropsychological profile of apathetic patients with MCI who have converted to AD gives interesting insight into the neuroanatomy of apathy. Robert and colleagues showed that an apathetic MCI group performed significantly worse in free recall memory tests, without concomitant deficits in other tests of executive functions\(^3\), in contrast with previous evidence from more advanced demented patients\(^{30}\). We believe that an executive default in activating strategies for retrieval from episodic memory might be a suitable explanation for these findings. Nevertheless, another possible interpretation is that apathy and free recall memory deficits are not related in terms of pathophysiology, but instead, their co-occurrence in MCI patients with higher conversion rates to dementia, might be an expression of additional AD type pathology, extending from medial temporal lobe to basal forebrain involvement.

We propose that in early stages of AD, apathy may be the result of a dysfunction of affective-emotional processing, which takes place in ventromedial PFC, i.e. medial orbito-frontal cortex (OFC) and ventral medial PFC, and its connections with amygdala and nucleus accumbens, leading to impairment in striatum dopaminergic activation. In fact, it has previously been shown that neuropathological progression in AD, targets the ventromedial portions of frontal as early as temporal cortex, with the exception of entorhinal portions, and precedes parietal and lateral frontal cortex involvement\(^{55}\). Indeed, recent evidence with positron emission tomography using Aβ tracer \(\left[{\text{[11C]}}\right] \)-“Pittsburg compound –B” (PIB) in mild and very mild AD dementia disclosed early frontal pathology, especially in ventral portions\(^{51}\).

**Apathy, Alzheimer’s disease and other cortical dementias: neuropathological and neuroimaging data**

Both pathological and functional imaging studies have implicated anterior cingulate cortex (ACC) and orbito-frontal cortex (OFC) in apathy associated with dementia, especially AD. Pathological data from AD patients with severe dementia disclosed correlation between ACC pathology and apathy severity, according to NPI scores\(^{52}\). These findings were recently replicated in structural magnetic resonance imaging data\(^{53}\). Additionally, a series of studies with single photon emission tomography (SPECT) have shown resting hypometabolism in ACC from AD apathetic patients when compared to non-apathetic individuals\(^{54-58}\). These findings are in agreement with experimental research ascribing a pivotal role to ACC in the human decision-making process\(^{59}\). Some of the same researchers also found hypometabolism in OFC regions, in addition to ACC dysfunction\(^{56,57}\). Lanctot and colleagues found similar results, showing decreased metabolism in left ACC and right OFC in AD apathetic patients scanned with SPECT\(^{60}\). More recently, Marshall and colleagues, employing PET in AD patients with mild to moderate dementia, showed that apathy was related to hypometabolism in ventromedial PFC, including the ventral ACC and medial OFC\(^{61}\), as predicted and described below in our proposed account for neurobiology of apathy in AD. PET data from frontal variant of frontotemporal dementia (fvFTD) has also shown a significant relationship between apathy and OFC hypometabolism\(^{55}\). It should be stressed that given decision-making is a dynamic process, resting PET or SPECT may lack the optimal spatio-temporal resolution to infer the underlying behavioral neurophysiology\(^{62}\), and may have higher sensitivity in more advanced stages of dementia. However, most of the functional neuroimaging data available so far display few conflicting issues and point to ventromedial PFC dysfunction as the background of apathetic behavior in cortical dementias. These data are in accordance with non-human primate and rodent research, and also fMRI in human studies, which strongly advocate the involvement of medial orbito-frontal regions and medial portions of PFC, especially ACC, in the human decision-making process\(^{64}\).

**Ventromedial prefrontal cortex and dopamine: decoding decision values and their translation into action**

There are several issues that must be considered when a subject engages in a decision-making process. He/she should be capable of attributing value to potential outcomes; any desired goal must have a reasonable probability of achievement; biologically relevant outcomes must be reasonably predictable; a plan of action must be selected in order to pursue reward or otherwise avoid punishment; the subject must discern not just the appropriate response but also the timing to execute it and the optimal response rate; and finally, demanding efforts and any delay to goal achievement must be factored in as action cost. Once this sophisticated processing concludes, top-down activation of behavioral output structures must
take place. These statements are based on an economic point of view and provide a useful framework to understand animal decision-making.

Data from non-primate research on decision-making suggests that OFC is critically involved in the prediction of reward outcomes, but not in the computation of outcome value. Conversely, the medial PFC, especially rat pre-limbic and infra-limbic regions, has been associated with outcome value learning and encoding, in addition to dorsomedial striatum and basolateral amygdala. Nevertheless, primate single-unit neuron recordings and human functional neuroimaging studies have clearly shown that medial OFC is involved in outcome value encoding, even when accounting for subjective preferences. Furthermore, the pattern of connections between primate medial OFC resembles that of rat medial PFC, suggesting that humans ventromedial PFC, including OFC, incorporated the outcome value processing ascribed to rat pre and infra-limbic medial frontal cortex.

Additional support for this claim comes from human studies showing that reward predictability activates more lateral portions of OFC, a region connected to the medial OFC network, which receives heavy inputs from different sensorial modalities, especially visual associative cortex.

ACC has been repeatedly involved in primate decision-making task. Its role has been ascribed to a wide range of activities: conflict monitoring, error monitoring and detection, response selection, attention control, pain affective processing, social cognition, reward probability processing and autonomic activation. The reason for the high number of proposed functions remains poorly understood. However, a possible explanation derives from the acknowledgement that ACC is both structurally and functionally heterogeneous, having a wide range of connections with other PFC regions, subcortical limbic, and motor output structures. There seems to be a dorsal/ventral and a rostral/caudal specialization within the ACC. Current understanding regarding ACC in decision-making suggests that this region is critically involved in adaptive learning of decision values in a changing environment. Kennerley and colleagues have shown that monkeys with ACC lesions fail to make the optimal decision choices based on previous gain and losses, when reward/action contingencies are manipulated. Furthermore, Behrens and colleagues presented compelling evidence of ACC activation in tasks simulating naturalistic settings of “environmental volatility”, whereby reward probabilities were dynamically manipulated.

The optimal computation of decision values must take into account several reward features, such as magnitude, contextual valence, predictability and probability; and lastly, the costs necessary for goal achievement. Rat experimental research suggests a pivotal involvement of ACC in effort-related decision-making. Indeed, Rudebeck and colleagues described this issue by showing a double dissociation between OFC and ACC, when processing delay and effort costs of actions. OFC lesioned rats displayed impulsive choices, being unable to wait for larger food reward; conversely, ACC lesioned animals had normal delayed responses but impaired effort-based decision-making, avoiding increased effort choices even though reward was four times higher.

Hence what could produce the link between OFC and ACC processing of decision values and subsequent activation of motor output structures?

Dopamine plays a critical role in determining response rates in reward-related behavior and is essential to effort-related decision-making. Dopaminergic antagonist infusion either systemically or within the nucleus accumbens substantially reduces response vigor in food seeking behavior or, otherwise bias action selection away from effortful choices, even when reward offers are considered worthy. It is well known that patients under high dopamine receptor antagonism can display severe apathetic behavior. Further support for this notion is found in non-primate research on drug seeking behavior reinstatement, which is a suitable model of drug addiction relapse after a period of abstinence. When triggered by stress, drug cues or drug per se, reinstatement constitutes a highly motivated behavior, and is virtually abolished by lesions in ventral tegmental area or dopamine antagonist infusion into dorsal striatum. Additionally, human functional neuroimaging data suggest that the intense desire that motivates drug seeking depends on primary processing of drug-related cues in OFC.

In a recent paper entitled “How the brain translates money into force”, Pessiglione and colleagues submitted individuals to an incentive-force task, whereby images of three different amounts of monetary rewards could be earned by a strong hand-gripping response. They found that greater offers of money correlated with higher scores on grip force and skin conductance. These motivational measures were also strongly correlated with ventral striatum activation, where nucleus accumbens lies. Using the same experimental paradigm, Schimdt and coworkers showed that patients with bilateral basal ganglia lesions, and Parkinson’s disease patients on L-dopa deprivation, displayed impaired incentive motivation behavior, again implicating dopamine and striatum in translating value into action.
The accumbens role in incentive processing has been further clarified in another recent study. Cooper and Knutson, submitting humans to an incentive monetary task, have found accumbens activity corresponding both to valence, that is gain vs. loss trials; and salience, i.e. uncertain vs. certain outcomes. A salient stimulus signals that a response will be necessary in the near future, that is, approaching an unexpected reward or running away from an environmental danger. This dual process account of accumbens function in incentive motivation behavior, suggests instead, that this structure may be a critical node in a circuitry, through which PFC processing of biologically significant stimuli, either valued or salient could trigger down-regulated structures in order to select the most appropriate response.

Belin and Everitt, using a behavior paradigm of drug seeking reinstatement in rodents, found evidence that could bridge the gap between value assessment in PFC and activation of output structures, such as fronto-striatal circuits. Their findings implicated ventral striatum as a critical node link to midbrain dopaminergic activation of dorsal striatum. This study seems to give the first functional supporting evidence for Haber’s proposed model of serial connectivity from ventral to dorsolateral striatal regions, through the midbrain dopamine system: the so-called striato-nigro-striatal spiraling connections. According to this model, ventral tegmental area receives input from the accumbens and projects back both to ventral and central striatum, which in turn projects back to midbrain, into substantia nigra, where classical nigrostriatal afferents arise towards dorsal striatum.

CONCLUSIONS

Pooling functional neuroimaging evidence from ventromedial PFC hypometabolism displayed by apathetic AD patients together with experimental data implicating this region in decision-making, we propose a mechanism for reduced activation of goal-directed behaviors in these patients (Figure). Dysfunction of action/outcome evaluation, executed by OFC, ACC and basolateral amygdala interactions, compromise optimal computation of outcome value, probability and action-related costs. This deficit disrupts appropriate transmission of decision value signal into nucleus accumbens, determining no activation of the midbrain dopaminergic ascending pathways, which are necessary for the engagement of dorsal striatum. Deprived of appropriate dopamine signaling, the latter structure becomes deficient in extracting the most appropriate response to be executed from intersected fronto-striatal circuits,

Figure. Proposed model of ventromedial PFC top-down influence on behavior generation. OFC, orbito-frontal cortex; ACC, anterior cingulate cortex; BLA, basolateral amygdala; NAc, nucleus accumbens core; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; DS, dorsal striatum; DLPF, dorsolateral prefrontal.
of goal-directed behavior, it is reasonable to hypothesize that enhancement of dopaminergic neurotransmission might improve apathetic symptoms. Indeed, there are anecdotal successful reports using this pharmacological strategy. Accordingly, Czerniecki and coworkers showed in a recent open label trial that Parkinson’s disease patients, submitted to subthalamic nucleus stimulation, had unequivocal improvement in apathetic behavior measures after treatment with dopaminergic agonist. Nevertheless, there is a need to test this hypothesis using a clinical trial design, and recruiting a reasonable number of subjects with clinically meaningful apathy. It is worth noting that this approach might not be successful if cognitive impairment is severe enough to compromise the executive elaboration of a goal-directed plan, as should be observed in more advanced demented subjects. It is also possible that cognitive improvement might explain the positive effects of cholinergic therapy on apathy measures of AD patients.

This model also predicts that apathetic behavior should be related to cognitive abilities attributed to OFC, such as reversal learning, and that sympathetic arousal should also be disrupted, which could easily be tested in future research. Obviously, this hypothetic model of ventromedial PFC dysfunction in AD apathy remains speculative and requires experimental confirmation, preferentially with functional neuroimaging techniques, employing reward related behavioral tasks, as has recently been studied in mania, psychosis, obsessive compulsive disorder, and pathological gambling. Employing new research methodology, it would be no surprise to find distinct subtypes of apathetic patients, as has been previously suggested. Unoubtedly, this effort could provide great insight into apathy neurobiology, aiding the development of new therapeutic strategies for this disturbing behavior in a wide range of neuropsychiatric disorders.

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