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Review

Auto-Activation Deficit: A Basal Ganglia Related Syndrome

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We draw attention to a new syndrome related to basal ganglia pathology. It is characterized by a deficit in spontaneous activation of mental processing, observed in behavioral, cognitive, or affective domains, which can be totally reversed by external stimulation that activates normal patterns of response. In addition, patients with auto-activation deficit (AAD) typically express the feeling that their mind is empty when they are not stimulated, a symptom that is sometimes difficult to recognize. AAD, also designated "psychic akinesia,"[1] differs from the inertia or abulia observed in patients with frontal lesions in that behavioral, cognitive, and emotional abilities become normal under external stimulation. This is particularly striking for executive functions which are essentially preserved under test conditions. The dramatic effect of external stimulation on these patients may appear to resemble what has been called "kinesia paradoxica" on a motor point of view,[2] except that, in the present case, external stimulation always activates all aspects of behavior. The syndrome is mainly encountered following lesions of the basal ganglia and is thought to result from the disruption of passing fibers mediating the internal activation of mental processing. We believe that the concept may generate some new lines of research into the non-motor roles of the basal ganglia such as behavioral activation, cognitive processing, affectivity, and conscious awareness.

CHARACTERISTICS OF AUTO-ACTIVATION DEFICIT

Inertia

Inertia is the most prominent feature of patients presenting AAD. They tend to stay in the same place all day long, sitting on a chair or lying on their bed, taking no initiatives and asking no questions, although they answer questions appropriately. They do not move around or engage in spontaneous activity. For example, the first description of the syndrome concerned an active businessman who became dramatically inactive following an encephalopathy caused by a wasp bite.[3] He did almost nothing all day long and expressed no sign of interest in anybody. Later, he became capable of routine activities such as buying a newspaper, reading it quickly, and watching TV, but he remained inactive most of the time. When stimulated, however, he was able to perform more complex activities, such as playing high level bridge. He was not bored by his condition, but it surprised him. The motor inactivity of patients with AAD may be just as spectacular. Ali-Cherif et al.[4] reported a patient who stayed on his bed for half an hour with an unlit cigarette in his mouth. When asked what he was doing, he responded: "I am waiting for a light." The same type of behavior was reported by members of the patient's household.[5] Trillet et al.[6] described a patient who spent 45 minutes with his hands on a lawn mower, totally unable to initiate the act of mowing. This "kinetic blockade" disappeared instantaneously when his son told him to move. It is important to note that none of the patients reported with AAD have a parkinsonian syndrome. Immobilization cannot therefore be confused with either a freezing or a motor akinesia. Patients with AAD do not try, or do not want to move, but they can move without difficulty when incited to do so.

Effect of External Stimulation

The most striking feature of this behavioral inertia is that it can be reversed. Indeed, it has been recognized for some time that the performance of patients with frontal lobe lesions can also be improved by interaction with the examiner who helps them focus their attention or provides a framework for executing tasks.[7,8] The mecha-

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nism of activation in patients with AAD seems simpler since a mere incitement can allow them to perform normally not only routine or overlearned activities but also complex behaviors. Global efficiency, assessed with the WAIS and the Raven's Progressive Matrices, is generally normal.[9] Patients with AAD, however, may have impaired performance in specific tests assessing executive functions, mainly because they have difficulty activating strategies or maintaining a mental set. This would explain, for example, their decreased lexical fluency and free recall performance in episodic memory tests or the increased number of non-perseverative errors in the Wisconsin Card Sorting Test, although they can normally generate the sorting categories. The dysexecutive syndrome may also account for some of the bradyphrenia occasionally observed. The syndrome is discrete, however, since no abnormal imitation, prehension, or utilization behaviors are currently observed. Generally speaking, the mental potential of patients with AAD is virtually unchanged but is not spontaneously mobilized. They do not spontaneously activate plans but, if pressed, can do so effectively.

Mental Emptiness

Inertia may be associated with the most enigmatic symptom encountered in these patients: mental emptiness. It is surprising that subjects who are cognitively unimpaired can remain inactive for hours without complaining of boredom. Their mind is "empty, a total blank," they say. In the most typical cases, they have no thoughts and no projections in the future. Although purely subjective, this feeling of emptiness seems to be a reliable symptom, since it has been reported in almost the same terms by numerous patients.[4,5,10,11] This symptom may provide an important clue to the nature of AAD, in that it suggests that mental life really fades during the periods of "aloneness" and is revived by stimulation. Not all patients with AAD experience this surprising mental vacuum, but those who do not report this state are unable to account for their inactivity. It may be that there are degrees of AAD. Alternatively, not all patients may have the same capacity for introspection or expression.

Stereotyped Activities

Despite their decreased overall activity and their initiation disorder, some patients may engage in repetitive and stereotyped activities. These "compulsive behaviors" can be mental (generally arithmomania,[5] such as mental counting of all the objects in their environment, or a repetition of mandatory sentences[12]), or motor (snapping or sucking the fingers, repetitive finger movements, shouting, hand-clapping). A patient with bilateral hypodensities of the internal part of pallidum following a brain anoxia complained of compulsive activities. He had to tap repetitive sequences of six with a pen or a cigarette lighter, to alternately open and shut every door that he saw for periods of as much as 10 to 15 minutes, to swallow each time that he crossed a line on the pavement or each time the bus passed a tree (personal communication). These stereotyped activities may even be more elaborate, as in the case of an amateur artist who, over a period of weeks, repeatedly painted the same type of subject: castles, ruins, historical portraits, etc.[1] Patients may therefore present the same compulsory and anxious features as in classical obsessive-compulsive disorders.

Affect

Affectivity is subject to a similar disruption of auto-activation. Affect usually appears flattened and emotional responses are blunted. Although the patients can correctly and critically assess their situation, they are not subject to self-depreciation. They admit that they have become a burden to their family but without an appropriate emotional response. They are not anxious, they express neither fear nor desire, but sometimes a vague hope of recovery, which seems more intellectual than deeply felt. Although at first glance, their affectivity seems spontaneously flat, they can generally react appropriately to good or bad news. But the reaction is short-lived and they rapidly return to their usual "neutral" state. In other words, events lack "resonance" in their mind and they appear to have no feelings when left alone.This suggests that the areas of the brain involved in affectivity and emotion are under the control of the same auto-activation system. If so, affectivity might not be the only initiator of behavioral responses. Intuitively, one would expect such an emptiness of the mind to preclude depression, which seems to require a capacity to project anxiously into the future or to ruminate. However, some patients do in fact also suffer from true depression. Danel et al.[11,14] reported three cases with bilateral lacunae of the basal ganglia who suffered major depressions associated with AAD. It appears then that AAD and depression can coexist, and that it is therefore possible to experience concurrently both mental pain or anhedonia and an empty mind. The severe inertia observed in patients with major depression associated with melancholia and stupor supports this hypothesis.

In conclusion, it might be said that the mind of patients with AAD is on stand-by when they are alone, but recovers almost all of its capabilities when stimulated by social interactions.

NEURAL BASES OF AUTO-ACTIVATION DEFICIT

Lesions

The only available data are those obtained from computed tomography (CT) scan and magnetic resonance imaging (MRI) studies. The first patients described with AAD had bilateral lesions of the lenticular nuclei.[3–5] The relationship between AAD and the striatopallidal complex was recently confirmed by a meta-analysis of behavioral changes following lesions of the basal ganglia. Six out of the seven patients with pallidal lesions were reported to have aboulia, and the other an obsessive-compulsive disorder, and half of those with caudate lesions (17 out of 33) also had behavioral inertia. However, none of the patients with lesions of the putamen presented such behavioral changes.[15] Positron emission tomography (PET) studies in patients with AAD[9] showed a slight but significant hypometabolism of the frontal cortex, attributed to a diaschisis induced by basal ganglia lesions. AAD has also been described in patients with bilateral lesions of the thalamus[16] in who a similar frontal hypometabolism was observed by SPECT, and in a patient with large frontal lesions.[17] Damasio and Van Hoersen[10] described a form of mental emptiness in a patient with bicingulate and SMA lesions, although external activation was not very effective in this case. AAD has also been reported in patients with unilateral lesion as well.[15] Therefore, the necessary and sufficient condition for AAD to appear is damage to striato-thalamo-prefrontal loops.

Proposed Underlying Mechanisms

It is not surprising that the basal ganglia, and more precisely the striatopallidal complex, play a role in non-motor processes, given their well-documented involvement in working memory[18] and in anticipation of reward [19] in primates. Studies in man also have demonstrated their implication in processes higher than motor execution and motor control. Firstly, the basal ganglia mediate response initiation and activation. Akinesia, the prototypical symptom of the basal ganglia, may result from a motivational deficit as well as the inability to "energize" the appropriate groups of muscles.[20] Secondly, there is evidence that they play a role in the maintenance of mental or cognitive strategies.[21] Unlike patients with lesions of the frontal lobes, who have difficulty finding new rules and a tendency to perseverate on previously activated mental sets, those with lesions of the striatopallidal complex have difficulty maintaining the rules that they have elaborated.[22] Finally, and in line with the latter finding, one of the main functions of the basal ganglia is to be involved in the automatization of procedures.[23] The role of the basal ganglia might therefore be in the automatization and maintenance of a new set of responses. The proceduralization of response schemas, controlled by the basal ganglia,[23–25] is essential to free the attentional resources of the prefrontal cortex to elaborate responses needed by new situations where no routine procedures can be activated. In basal ganglia disorders, since previously elaborated procedures cannot be engaged, the patients must draw on the constant maintaining of the voluntary control of attention that decreases the attentional resources of the "supervisory attentional system."[26] This might account for some of the differences that are currently observed between lesions of the prefrontal cortex and basal ganglia.

The study of patients with AAD shows that the basal ganglia are part of a neural network implicated in activation of brain processes that includes the striato-thalamo-prefrontal circuits. The mechanism by which the basal ganglia intervene depends on the anatomo-functional model to which we refer. One of them relies on the description of five discrete parallel circuits in the monkey,[27] that each links a specific prefrontal cortical area to a discrete zone in the striatum. Accordingly, the pathways linking the ventral striatum to the anterior cingulate cortex and the ventral part of the caudate nucleus to the orbitofrontal cortex are good candidates for a role in psychic auto-activation since: (1) neuronal activity in the ventral striatum and caudate nucleus is increased by anticipation of a subsequent positive event;[28,29] and (2) recordings of orbitofrontal neurons in monkeys indicate that they provide motivational components for the control of goal-directed behavior.[30] Human data also seem to support this view. The most important observation was probably that of Damasio and Van Hoersen[10] who discribed a female patient with bilateral lesions of the anterior cingulate cortex and SMA. Over a period of several months, the patient presented a quasi-akinetic mutism. After some improvement she explained that she had nothing to say during this phase and that she had an "empty mind." A series of three patients with unilateral (right or left) ablation of the SMA and the adjacent part of area 24 gave the same picture of akinetic mutism, but for only a few weeks.[31] These patients also declared that if they remained quasi-mute, it was because they had nothing to say. Even though they were not asked more precise questions about their mental activity, their disorder appears to resemble AAD. There are, however, some differences that may be important, and notably that in all four cases, external activation was largely ineffective. These observations suggest firstly that the cingulate cortex is a relay in the neuronal network of auto-activation,

and secondly, that the cingulate cortex may also mediate external activation, although it cannot be excluded that it was the associated lesion of the SMA, another major component of the frontobasal circuits, which accounted for the AAD. Interestingly, a patient with a bilateral lesion of the anterior cingulum that spared the SMA[32] had a severely blunted affect, but her behavior was conspicuously distinct from AAD, consisting of permanent hyperactivity with severe distractibility. Thus, it is difficult to construct an anatomical model that would integrate all the data derived from cortical and subcortical lesion studies. Furthermore, the model of parallel and independant circuits does not take into account the massive convergence of the striatal efferents onto the pallidum,[33] which certainly plays a specific role. The pallidum is not just a relay but a structure that filters, selects, and integrates pieces of information, whatever the domain of the information, i.e., motor, cognitive, behavioral, and affective. The consequence of a pallidal dysfunction might therefore be an activation deficit that may affect a number of brain functions.

WHAT ABOUT EXTERNAL STIMULATION?

The concept of AAD implies, per se, that external activation remains possible. When a disruption of external activation is associated with AAD, it results in akinetic mutism or a vegetative state, both of which are virtually impossible to investigate. However, some aspects of catatonia may be considered as resulting from a deficit of external activation, and individual cases may exceptionally provide an opportunity to study the partial loss of external activation associated with AAD. One such case was a 19-year-old woman in a pseudo-catatonic state after cerebral anoxia due to cardiac arrest. She appeared motionless, like a statue. Her face was completely immobile and expressionless. There was no resistance to imposed movements but she tended to remain in a cataleptic position. She stared directly ahead, had no pursuit movements, and did not move her eyes when addressed. Verbal stimulation had no effect and she remained mute. Interestingly, emotion was from the beginning a remarkable stimulus. She turned her eyes and head on hearing the voice of her mother in the corridor. When asked if what her mother said was true, namely that her condition made her suffer, her eyes filled with tears although her face remained impassive. Yet, videotapes recorded by her parents displayed expressive attitudes of laughter, joy, and cheerfulness in appropriate circumstances, especially when she was in contact with her dog or horse. In other words, she lost her statue-like appearance only when strongly stimulated by affective situations. And indeed, external activation seems to be related to the affective value of the stimulation, since it is only obtained by interaction with living creatures, never with objects. External activation may be, therefore, mediated by the circuits of affectivity.

This patient had three bilateral lesions on MRI scan: one at the tip of the globus pallidus, similar to lesions found in some patients with AAD, and two junction infarcts affecting the frontal and parieto-occipital regions. Since there is no reason to suspect that the parieto-occipital lesion played a role in this matter, we propose that the frontal lesions in the dorsolateral cortex and the underlying white matter might be responsible for the deficit in external activation. This is consistent with the suggestion of Mesulam[34] that the dissociation of internal and external activation can be explained in terms of ontogenic and phylogenic development. This hypothesis is based on the demonstration by Sanides[33] of two main trends in structural development of the prefrontal cortex: a medial archicortical trend originating in the periarchicortical proisocortex of the medial wall of the frontal lobe, giving rise to the anterior cingulate cortex and SMA, and a lateral paleocortical trend beginning in the peripaleocortical proisocortex of the insula. The connectivity of each of these regions is specific and suggests that the medial paralimbic system is involved primarily in self-initiated actions from the inner source, whereas the lateral system is involved in environmental responses. If so, our patient may suffer not only from a disruption of auto-activation caused by the bipallidal lesions but also from deficit of external activation caused by bilateral lesions disconnecting the two dorsolateral prefrontal cortices. The preservation of affective reactions could be due to the fact that the anterior cingulum was spared.

The fact that, in this patient, only emotion could produce a response is interesting in that it suggests that there are several mechanisms of activation. One is triggered by emotions and is mediated by structures including the anterior cingulum. Another is triggered by external, environmental stimuli and is mediated by structures including the dorsolateral frontal cortex.

IS AAD A HEURISTIC CONCEPT?

We believe that AAD may help to understand the role of the basal ganglia. It shows that: (1) the basal ganglia are not only involved in *motor* control and execution; (2) the non-motor functions of the basal ganglia are not limited to the cognitive domain, i.e., the executive functions, as suggested by the analysis of patients with degenerative diseases; and (3) one of the roles of the basal ganglia is to activate, to initiate or to control "responses," whether motor, behavioral, cognitive, affective, or emotive.

The term auto-activation has clear connotations in terms of autonomy. As a first approximation, it might be suggested that the global handicap of patients with AAD corresponds to a lack of will. The circuits mediating auto-activation would thus appear to be those of volition. However, when patients with AAD are "heteroactivated," they also feel that they are acting freely and voluntarily. Thus, the results of both auto- and external activation are experienced consciously as autonomic actions. Another interesting outcome of the study relates to "conscious awareness." Patients with AAD remain with an empty mind while in the waking state. They describe a mental state, that, to our knowledge, has never been reported, and which is almost unimaginable to a normal conscious human being: conscious awareness without any content, i.e., consciousness per se.

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