Negative dimension in psychiatry. Amotivational syndrome as a paradigm of negative symptoms in substance abuse

Dimensioni negative in psichiatria. La sindrome amotivazionale quale paradigma di sintomi negativi nell'abuso di sostanze

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SUMMARY. Negative symptoms, conceptualized as clinical manifestations of schizophrenia, and subsequently described in other psychiatric disorders, include the loss of normal arousal, drive and affective reactivity. In the field of substance abuse, an interesting analogy can be detected between negative symptoms, in their classical meaning, and the amotivational syndrome (AS), which has been described as a form of chronic cannabis intoxication. AS also shows a close resemblance to the reward deficiency syndrome (RDS) of alcoholics and stimulant abusers, and to the post-withdrawal syndrome (PWS) of detoxified heroin addicts. A variety of substances share a common tropism for the dopaminergic system, leading to a state of hypophoria, which seems to represent a common pathway for chronic substance abusers. In the light of these convergences, a common treatment principle for addictive disorders can be enunciated. This consists in resorting to pro-dopaminergic drugs, that are supposed to replace damaged functions and control craving, and in avoiding anti-dopaminergic drugs, that are expected to exacerbate craving and impede the reversal of the reward deficiency.

KEY WOKDS: negative symptoms, amotivational syndrome, reward deficiency syndrome, hypophoria.

RIASSUNTO. I sintomi negativi, concettualizzati nell'ambito della schizofrenia, e successivamente riscontrati in altri disturbi psichiatrici, comprendono la perdita dei normali livelli di attivazione, iniziativa e affettività. Nel campo del disturbo da uso di sostanze esiste una analogia tra sintomi negativi, intesi nella loro accezione classica, e sindrome amotivazionale (SA), specifica dell'intossicazione cronica da cannabinoidi. A sua volta la SA mostra strette relazioni con la sindrome da deficit di reward, descritta negli alcolisti e nell'uso di psicostimolanti, e con la sindrome d'astinenza post astinenziale (SAPA) descritta per la dipendenza da eroina. Sostanze d'abuso diverse mostrano, dunque, una azione comune che converge sul sistema dopaminergico conducendo a uno stato di ipoforia. Alla luce di questa convergenza appare indicato, nel trattamento a lungo termine della dipendenza da sostanze, l'impiego di farmaci psicotropi dopaminergici che sostengano il sistema del renard, e controindicato all'opposto l'impiego di neurolettici, che lo antagonizzino.

PAROLE CHIAVE: sintomi negativi, sindrome amotivazionale, sindrome da deficit di reward, ipoforia.

NEGATIVE DIMENSIONS IN PSYCHIATRY

Negative psychiatric symptoms were originally conceptualized as part of one of the two major psychoses, schizophrenia. That cluster of features corresponds to the loss of normal arousal, drive and affective reactivity. In other words, they represent what the patient is lacking, and thus stand opposite to positive symptoms, which loom as something in excess, or in addition to normal functions, both as regards perceptions (hallucinations) and thought (delusions).

On the whole, negative symptoms can be summed

up as a state of detachment and disengagement from the environment. The development of negative symptoms starts early in the course of schizophrenia, proceeds gradually and is often associated with typical depressive symptoms, eventually resulting in a state of affective numbing and flattening of emotions that gives a poor response to pharmacological treatment (1).

Later on, negative symptoms have been conceptualized as a dimension featured by different disorders. As a result, interest rose in the evaluation of negative symptoms within the clinical picture of bipolar disorders and obsessive-compulsive disorders, and also in degenerative neurological disorders such as dementia and Parkinson's disease, and vascular-related damage (stroke) (2,3). Moreover, researchers have been looking further into the difference between negative symptoms and concurrent features of cognitive impairment, so that the concept of "negative" functioning has extended to embrace negative affects and cognitive deficiencies (4,5).

Several authors have pointed out that some symptoms, such as apathy, abulia, anhedonia and social isolation are shared by depression and schizophrenia (6,7): this overlap between two major psychotic conditions suggests that negative symptoms are an expression of a general psychotic process rather than a specific feature of either clinical picture (8,9).

In any case, negative symptoms show a different response to pharmacological treatment: the introduction of antidepressant treatment following the discontinuation of neuroleptic medication is followed by a sharper reduction of negative symptoms in depression affecting schizophrenic patients (10).

In major depression, which, in comparison with other mood disorders, mostly features negative symptoms, those symptoms weigh as negative prognostic factors, especially as regards affective indifference, the sensation of an empty brain (thoughtlessness), and lack of drive (abulia) (11). Negative symptoms and cognitive impairment have also been reported in pictures of pathological grief, which, on clinical grounds, stands half way between depression and post-traumatic stress disorder, but is classified as an autonomous disorder (12). Pathological grief can follow the loss of a significant other through the dynamics of attachment (13); it also features avoidance and mumbling as a consequence of a reduced ability to elaborate the body of information that is associated with the loss that has been experienced (14,15). As far as negative symptoms are concerned, pathologic grief is characterized by social and job-related impairment (16). In particular, the reduction of memory is greater in pathological grief than in depression or post-traumatic stress disorder (17). Memory impairment has also been described in the obsessive-compulsive disorder, together with the disturbance of procedural functioning which is surely implied by that condition. Memory appears to be hampered as a consequence of the abnormal arrangement and the encoding of information at an output level. The most common cognitive features of this type are the prolonged latency of answers, the perseverance of wrong reactions to stimuli, and the awkwardness of adaptation to change on the basis of registered feedbacks (18). Such abnormalities were mapped as pertinent to the function of the frontal lobes and basal ganglia (19).

In the field of substance-use disorders, an interesting analogy stands out between classic negative symptoms and the amotivational syndrome (AS) displayed as an expression of chronic cannabis intoxication. We will mainly focus on the AS and its links with the reward deficiency syndrome (RDS), originally described as a sequela of chronic alcohol and stimulant abuse. These two latter conditions are closely related too to the post-withdrawal syndrome (PWS) described by Martin and colleagues as an enduring pathologic state in abstinent detoxified opiate addicts (20-22). Bearing in mind the AS model, some of its prominent negative symptoms can be hypothesized as constituting a common endpoint of late clinical pictures linked to chronic intoxication by various substances of abuse.

AMOTIVATIONAL SYNDROME AND ITS NEUROBIOLOGICAL BASES

AS is one major complication of chronic exposure to cannabis, and combines the flattening of affects and elements of cognitive impairment similar to those displayed in schizophrenia and depression. It is characterized by gradual detachment from the outer world, and loss of emotional reactivity, drives and aims. Responsiveness to outer stimuli is blunted, and subjects are unable to experience or anticipate any pleasure except by using cannabis. Memory and attention are hampered (23) (**Table 1**).

Affected subjects have a poor level of school-related functioning, are less satisfied with their educational activities, and easily enter into conflict with scholastic authorities. Both cannabis consumption itself and a cannabis-related environment are thought to contribute to the cognitive profile of AS (24).

A body of research has shown that the acute administration of tetrahydrocannabinoid (THC) increases metabolism in the ventral tegmental area by a CB1-mediated input, and causes an increase in dopamine

Table 1. Clinical characteristics of reward impairment in drug addicts

Post-withdrawal syndrome	Reward deficiency syndrome (23)	Amotivational syndrome (117)
Feelings of hypophoria (21)	Gradual detachment from the outer world	Social withdrawal
Dysphoria	Loss of emotional reactivity, drives and aims	Loss of impulse and motivation
Extreme sensitivity to pain	Blunted responsiveness to outer stimuli	Emotional detachment
Inability to complete even simple tasks	Inability to experience or anticipate any pleasure	Detachment from reality
Inability to experience pleasure through recreational or natural stimuli	Hampered memory and attention	Reduction in attention and memory

release to the shell area of the nucleus accumbens (25-27). This phenomenon has recently been confirmed in vivo in the human striatum by studies of functional neuroimaging that apply the positron emission tomography technique (28). Marijuana use increases blood-oxygen level dependence (29), which is related to a magnetic measurement of changes in the level of blood oxygen, and corresponds to various states of metabolic activation of specific brain areas engaged in the production of certain feelings or outputs. Two different cannabinoid receptors have been described in the human body. The CB1 type (30) is widespread in basal ganglia, the cerebellum and the hippocampus, and modulates the activity of the gabaergic, glutammatergic and dopaminergic systems, all of which are influenced by exposure to cannabis. By contrast, the CB2 type is expressed in the immune system (31).

Both in the animal model and in man, continued exposure to cannabis causes a change in neuronal functioning (27,32,33). The acute increase in dopaminergic release is followed by a reduction of dopamine in the same areas of the reward system. This phenomenon is likely to be linked both to the down-regulation and the desensitization of CB1 receptors (27,34-36). On clinical grounds, these changes appear to be related to the development of anhedonia and a loss of sensitivity to previously pleasant stimuli (37,38). The application of functional magnetic resonance imaging succeeded in linking chronic exposure to cannabis to an altered reward sensitivity (34). Although dopamine is by far the most studied neurotransmitter in terms of the issue of reward and motivation, it should be recalled that dopaminergic pathways are influenced by other receptorial systems, and intermingle with both opioid and cannabinoid systems (39-44). On the whole, the AS, or cannabis-related RDS, may be directly related to a change in dopaminergic function, in this case through a cannabis-induced modulation of the cannabinoid receptor activity.

SUBSTANCE USE AND REWARD-SYSTEM ACQUIRED ABNORMALITIES

A well-known paradigm of acquired reward pathology is the natural history of heroin addiction. The course of heroin addiction develops in three stages (45): the first stage is pleasant involvement in substance use (the "honeymoon" stage). In healthy, non-tolerant subjects, acute opiate administration produces a marked state of euphoria, coupling serenity and peacefulness with actual mood elation and reward. At this stage, substance use does not take place on a regular basis, and people express confidence that they can break the habit at any time if so wished. No full-blown addictive behaviour is displayed, the substance is self-administered at stable doses, and the desire to use it is not very urgent or compelling. In most cases, withdrawal has not yet been experienced. The possible risks are underrated both by the person and the surrounding environment, although the first signs of mood instability and a lowered threshold for affective distress can be detected. The second stage follows the "honeymoon" one, and corresponds to the phenomenon of self-administration at increasing dosages: the transition to regular substance use leads to the development of tolerance, so that the euphoric effects dwindle, while the opposite, withdrawal-related feature starts to recur and becomes more and more prominent. In order to restore the balance and reproduce drug-elated euphoria, subjects automatically increase substance dosages, but in so doing they also pave the way for heavier rebound symptoms. The desire to self-administer the substance has now become urgent and overwhelming, despite the reduced persistence, intensity and frequency of satisfactory drug-induced euphoric states. Eventually, subjects swing away from a state of normal liability concomitant with recurrent states of withdrawal or discomfort on account of the absence of drug-induced euphoria. By this stage, the

subject could be defined as a drug addict, because of his/her incapacity to change behaviour so as to reverse this undesirable condition and prevent relapses into it. Depending on a variety of factors, but especially as a result of the level most likely along the grade of addiction severity itself (craving, withdrawal) people get fully engaged in substance-seeking, by any available resource and by any means, no matter how hazardous or illegal it may be. The third stage is a series of stereotypically repeating cycles (the "revolving door" stage) featuring detoxification, temporary suspension of use with possible psychosocial recovery, addictive relapse and rapid impairment. At this stage, due to the increased difficulty of finding regular and consistent amounts of the substance, and to feelings of desperation about one's general condition, addicts resort to treatment facilities. What can be noted at this point is the "clean" part of the revolving door cycle, from an addictive viewpoint, in a way that is able to reverse tolerance and so cut down on drug-related expenses. At this juncture, a new cycle is ready to begin, contrary to the subject's expectation of being able to handle drug use from a condition in which craving is reset. Occasionally, deadly events interrupt the cycle, and this becomes more and more likely as cycles go by. Notably, the "clean", non-tolerant periods bear the highest risk of overdose-related deaths, especially when they are spent in artificial environments (46).

Within the framework of these three stages, the hedonistic-euphoric dimension, which was prominent at the beginning, is gradually replaced by a counterpolar state, characterized by anhedonia and hypophoria (lack of drive, motivation and reactivity with respect to what the person regards as being satisfactory). From a withdrawal-related point of view, through each detoxification cycle the patient passes from the acute withdrawal state (counterpolar to intoxication) to a later and enduring drug-free state featuring symptoms of hypophoria, looming as an acquired discomfort related to the absence of drug-related stimulation. Hypophoria includes somatic, vegetative and mental symptoms such as susceptible or irritable mood, amplified pain perception, inability to perform simple tasks and make normal efforts, and inability to experience reward in any way other than substance use. This syndrome closely resembles the subthreshold symptoms of dysthymia and the residual symptoms of chronic bipolar disorder (47).

In conclusion, the natural history of heroin addiction displays three stages, eventually leading to a chronic state of hypophoria, possibly interrupted by relapses, which recalls the features of the RDS described as a sequela of alcohol and stimulant chronic abuse (45). From a neurophysiological point of view, a variety of substances are involved in the dynamics of pleasure-feeling and reward, among which dopamine, gaba and opioids are the best known. Anatomic sites of pleasure-feeling and reward-seeking seem to correspond to brain areas known as the ventral tegmental area, the nucleus accumbens, caudate, and substantia nigra. Dopaminergic activity is concentrated in the accumbens, caudate and ventral tegmental area, which are referred to as the afferent arm of reward circuitry. Gabaergic activity, which has been shown to be considerable in the ventral tegmental area, and opioidergic activity in the substantia nigra and accumbens, also contribute to reward dynamics. Basic neurochemical events that correspond to reinforcement and reward take place in the brain areas just named (48-50).

Substances of abuse act upon specific receptors on neuronal cells, often mimicking the effect of endogenous equivalents. Thus, substance-inducing acute effects can be described as the stimulation of neuronal circuits corresponding to their endogenous equivalent. A number of studies (resorting to pharmacological parameters, neuroimaging, and microdialisis) have agreed on the fact that the acute administration of rewarding drugs causes a release of dopamine due to the projection of neurons with a cell body located in the ventral tegmental onto the post-synaptic surfaces of the nucleus accumbens, especially at the shell part level (51-53). This process normally takes place when people are exposed to salient stimuli, and underlies the dynamics of adaptation and selection of available sources of euphoric self-stimulation in one's natural environment. An increased availability of dopamine in the pre-synaptic gasp of the accumbens shell builds a memory of salience for certain stimuli, which are functionally related to survival, nutrition, reproduction, or relief, through such feelings as sexual arousal, competition, appetite or discomfort (54-56). In other words, salience is a basic way to bookmark rewarding stimuli as crucial to attaining one's aims sooner or to getting spatially closer to craved objects. As far as substance use is concerned, salience is the crucial node between the acute experience of substance-related effects and expected rewards from new episodes of consumption. Pleasant side-effects, environments and situations which happen to be associated with substance availability are registered as conditioning stimuli, so that they can cause reflected withdrawal and automatic drug-seeking behaviors, even in the absence of a direct craving for drug-related effects (57).

This learning process corresponds to changes in the structure of the brain (gene expression, neuronal structure and morphology) by the mechanisms of neuronal plasticity, particularly in memory-related areas (58-61).

Experimental research consistently indicates how such changes persist in the long term (62-65). These areas become sensitized to the presentation of drug-related stimuli, both in the animal model and in man, and they maintain that acquired sensitivity long after the latest exposure to the drug (62,65,66). Although dopamine release in the accumbens shell plays a crucial role in associative learning, other brain areas too are involved in the development of addiction starting from substance use. In particular, the anterior cingulated and orbito-frontal cortices at a prefrontal level mediate behavioural outputs produced by drug-related cues (67-70). Neuroimaging studies have clearly mapped the metabolic changes in specific areas associated with subjective craving and drug-related cueing: the extent of metabolic changes in the orbito-frontal and anterior cingulated cortex areas is directly related to the intensity of cue-induced craving (69,71-76). On the other hand, neuroimaging studies on brains of abstinent individuals with a history of chronic addictive use reveals a reduced level of baseline metabolism in the same areas (73,76-81). Such metabolic "depression" also includes responses to normal biologically relevant stimuli, such as food-related or sexual cues (68) and to decision-making challenges in certain experimental settings (82,83). In the striatum, both a lower level of available dopamine and a reduced number of D2 receptors have been documented (84-88). To sum up, chronically exposed individuals who have developed drug addiction show they are hypersensitive to drug-related stimuli, while they are less responsive to other sources of direct stimulation or cueing.

Other systems are relevant to addiction biology, such as the hypothalamic-pituitary-adrenal axis (HPA), which mediates response to stress. Substances of abuse stimulate the HPA axis, which can itself become involved in the process of reward and reinforcement of self-administration (89,90). Moreover, substance abuse and withdrawal are linked to the production and release of the corticotropin releasing factor (CRF) by extra-hypothalamic sites (91-94). Stressing stimuli may increase extra-hypothalamic CRF-producing activity, thus amplifying the reinforcing effects of drugs, appetition for them and addictive behaviours (95,96). It has also been documented that CRF-like factors are related to acute and long-term withdrawal, and to relapse proneness, along with the known clinical link between the low threshold to subjective stress and relapses in abstinent drug addicts (93,97-99).

On the whole, the dopaminergic system plays a crucial role in substance abuse and addiction. A number of research papers have indicated how cannabis, as well as other substances of abuse, share a dopamine-releasing action in the nucleus accumbens (the main node of the dopaminergic mesolimbic pathway) (27,51,100-104). Likewise, THC and other drugs (amphetamines, cocaine, alcohol, nicotine and heroin) share the property of selectively increasing dopamine release in the shell part of the accumbens, rather than its core (27,39,52,105,106). Alcohol has proved to increase dopaminergic pulsatility and a generalized increase in arousal and sensitivity to reward (76). Chronic cocaine use is also responsible for a reduced dopaminergic release in the accumbens (107).

Since all the different substances seem to share a common mechanism of action, they may be thought to share the feature of eventual damage too. Bowirrat et al. (108) argue that dopamine is the main neurotransmitter responsible for both the reward cascade common to all substances of abuse, and the AS: reduced dopaminergic activity underlies all conditions of chronic alcohol or drug administration, which correspond to reduced sensitivity to reward and decreased ability to cope with stress. Different substances own one specific neurochemical property linked to their direct molecular target (i.e. the cannabinoid system, gabaergic receptors for alcohol and benzodiazepines, the opioidergic system, cholinergic receptors for nicotine) and a common eventual effect on the dopaminergic system, with special regard to the reward pathway circuitry (108).

There is therefore no justification for using the concept of the AS or RDS to indicate one specific condition (chronic cannabis use), but a common clinical ground for all kinds of chronic abuse.

One could also hypothesize that the rewards of drug users are already impaired before drug use, on the basis of genetic dispositions to drug use, possibly involving the polymorphism of DRD2 receptors, a key element in the reward cascade (109). Blum et al. (23,110) have suggested that cannabis abusers may be characterized by a primary abnormality of the reward system, with a lower level of dopaminergic activity, which becomes normalized through exposure to cannabis. This view recalls the self-medication hypothesis of addictive disorders originally formulated by Khantzian (111) with respect to the addictive use of opiates and cocaine: in that case, specific emotional distress and mental disorders were hypothesized as the basis for involvement in regular drug use with a self-medicating purpose.

THERAPEUTIC IMPLICATIONS

On therapeutic grounds, AS, RDS and PWS, all developing as late consequences of intensive drug use,

achieve stability through a reduced dopaminergic metabolism in the reward system circuitry, and require the employment of specific-agonist drugs (opioidergic, cholinergic, gabaergic) and counterindicate the employment of functional antagonists of the reward-related dopaminergic system, for the purpose of reward rebalance. In other words, therapeutic medications should interact with the same targets as those of abused drugs, at a neurochemical level, in order to replace damaged physiological functions.

In the case of heroin addiction, for instance, methadone treatment can be seen as providing a general paradigm: methadone does replace impaired functions and prevents the PWS, does not impede the reprise of the dopaminergic metabolism and prevents further damage by the mechanism of narcotic blockade. Drugs like varenicline (cholinergic agonist) (112) and bupropion (cholinergic antagonist but dopamine agonist) (113,114) have been tried with some success in the treatment of nicotine withdrawal and nicotine dependence. Unlike varenicline, bupropion is not specific to nicotine, but acts upon the common reward pathway: its dopaminergic and noradrenergic actions are responsible for nicotine withdrawal symptoms and favour detachment from nicotine, although bupropion is not powerful in keeping craving under control in the longer term; at least at tolerated dosages, bupropion looms as the paradigm of dopaminergic agents and is capable of producing positive effects in drug abuse, regardless of a specific anticraving action, because of its action on the shared ground of a reduced dopamine-related function.

By contrast, the use of neuroleptic drugs should be applied with great caution in patients with a history of reward impairment, since they own a sharp dopamine-antagonist action. Atypical antipsychotics, despite their different profile of neurochemical action, may elicit or worsen reward impairment, though to a lesser extent, or interfere with dopamine metabolism by different pathways (115). Even if their use is recommended with respect to acute psychosis, those with low affinity and specificity (fast-off interaction dynamics from dopamine receptors) are preferable (116).

CONCLUSIONS

A variety of substances of abuse, despite their different mechanisms of action, converge on a common pathway centring on the circuitry of reward. The eventual damage produced by all substances involves dopaminergic dysfunction, mirroring the initial dopaminergic stimulation corresponding to euphoria and increased reward. In the case of cannabis, this picture has been described as the AS.

Adopting a longitudinal view, the course of addiction starts from the experience of hyperstimulation and this proceeds to overcoming dysphoria and loss of motivation. Deep changes in brain function and microscopic structure underlie these clinical grounds, and correspond to the concept of addiction as a unique metabolic disease, regardless of the meaning and clinical picture or earlier phases. The abnormal dopaminergic metabolism of the addictive brain implies the impairment of general reward capacity, also involving the same substance responsible for addiction, together with the ability to cope with stress and the lack of continuous stimulation.

We have tried to give a comprehensive description of the cannabis-related AS, the alcohol/cocaine-related RDS and the opioid-related PWS. These three clinical pictures, originally referred to three different classes of substances, share the feature of motivational loss, which looms as the specific acquired functional leak affecting the addict's brain. On therapeutic grounds, pro-dopaminergic drugs are to be regarded as useful, because of their positive impact on the hypotrophic dopaminergic system, while anti-dopaminergic drugs are to be avoided if possible, especially in long-term regimens.

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