SHORT COMMUNICATION

Neurobiology of motor impulsivity

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Abstract

Impulsivity represents a multidimensional construct including motor impulsivity as a conceptually and neurobiologically distinguishable subdimension. Motor impulsivity is linked to deficits in motor inhibition and represents a part of symptomatology in different neuropsychiatric disorders. However, recent classification systems are considered to lack a biological approach to psychiatry based on a precise definition of neurocognitive endophenotypes (such as e.g. motor impulsivity) and objective description of the symptomatology of neuropsychiatric disorders. We, therefore, summarize in this work the present knowledge about motor impulsivity and its neurobiological background.

Motor impulsivity

Impulsivity is closely related to insufficient inhibition. Therefore, historically, interrelated terms of will, inhibition and impulsivity were studied in different scientific disciplines, such as philosophy, psychology, (neuro) physiology, neurobiology and psychiatry. All recent definitions of impulsivity are multidimensional and sometimes considered to be very broad ranged even incompatible (Bari & Robbins 2013). They encompass different impulsivity subtypes, as defined by Evenden (1999): impulsive action, impulsive choice, reflective impulsivity and risky behavior and involve all the dimension of motor impulsivity (Durana & Barnes 1993, Moeller *et al* 2001).

Motor impulsivity results from insufficient motor or response inhibition, which is the most observable component of cognitive control. This impulsivity subtype is considered rather as a fast form of impulsivity (or unplanned behavior) which is predominantly triggered in a bottom-up way (Bari & Robbins 2013). Research evidence indicates that motor inhibitory processes related to motor impulsivity can be further subdivided neuroanatomically (Rubia *et al* 2001) and neuropharmacologically (Eagle *et al* 2008) in action restraint and action cancellation (Schachar 2007). The main difference between them consists in the stage of processing of a motor response. Action restraint represents the inhibition of a response before this has been started (withholding from responding assessed by the go/no-go (GNG) paradigm) (Band & Boxel, 1999). Action cancellation describes inhibition of a motor process at later stages of processing, during its execution (assessed by the stop-signal (SST) paradigm (Verbruggen & Logan 2008). Impulsive behavior is not stable (Wingrove & Band 1997) and can occur as a result of situational (state impulsivity) and dispositional (trait impulsivity) factors. It can be functional (if it helps the subject to adapt successfully to a complex and rapidly changing environment (Pattij & Vanderschuren 2008)) or, in extreme forms, in neuropsychiatric disorders (Chamberlain & Sahakian, 2007, Robbins *et al* 2012) dysfunctional (Evenden 1999). In connection to the psychiatric symptomatology, a dis-

tinction between two failures of response inhibition, namely motor impulsivity (related to the beginning of action) and compulsive actions (related to the deficient achievement of action), should be made (Robbins *et al* 2012).

In the past decades, it has been acknowledged that motor impulsivity, in its extreme forms, plays an important part of the symptomatology of impulse control disorders, such as: attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), schizophrenia (SCZ) (Lipszyc & Schachar 2010), trichotillomania and substance dependence (Chamberlain & Sahakian 2007). Also healthy relatives of these patients show response inhibition deficits. Therefore, response inhibition represents an important endophenotype in the research for genetics of these disorders. However, the classification systems (e.g. DSM-V) still lack precise and objective diagnostic criteria of these disorders, based on a neurobiological footing of cognitive endophenotypes (Robbins *et al* 2012), such as motor inhibition. This biological approach to psychiatry would have implications for future classification, diagnostic and therapeutics of neuropsychiatric disorders.

Neuroanatomy of motor impulsivity

Motor inhibition and related motor impulsivity involve motor-related cortical and subcortical brain areas (Bari & Robbins 2013), more precisely the fronto-basal-ganglia network (Chamberlain & Sahakian 2007), mainly in the right hemisphere (Aron 2010).This network is modulated by brain stern-cortical circuits (Dalley *et al* 2011).

To the main cortical areas mostly contributing to response inhibition belong (Aron 2010, Bari & Robbins 2013): pre- supplementary motor area (pre-SMA), supplementary motor area (SMA), primary motor cortex (M1) and right inferior frontal cortex (rIFC: BA 44, 45, 47/12). Pre-SMA is considered to contain „switch neurons" involved in go and no-go processes, their selection and mediation between prefrontal (rIFC, rDLPFC) and motor cortical regions. The SMA may be activated more in motor behavior by projecting to M1 (Mostofsky & Simmonds 2008). The activation of rIFC was repeatedly associated with response inhibition (Aron 2010). Interestingly, the hypoactivation of right fronto-basal ganglia network was associated with ADHD-related symptoms (Bari & Robbins, 2013). The activation of different parts of the network depends on involved hot (affective) or cold (executive) processes. The difference between response restraint and response cancellation seems to be only partial. Although both processes activate the above mentioned structures, the first tends to produce a bilateral and the second a predominantly right-sided activation. (Eagle *et al* 2008).

To the main subcortical structures involved in motor inhibition belong (Dalley *et al* 2011): thalamus (Th); basal ganglia (BG) including dorsal striatum (caudate-putamen), globus pallidus (GP) and subthalamic nucleus (STN); and locus coeruleus (LC). The BG structures project via Th to the PFC. The role of Th may be in gating, i.e. allowing or stopping the information issued from the communication between BG and PFC to reach M1 and execute the motor response (Bari & Robbins, 2013). Two different pathways including different subcortical structures have been supposed in the mediation of partially different inhibitory processes (Aron 2010, Bari & Robbins 2013). The first, called hyperdirect pathway, seems to mediate global, fast and reactive inhibitory mechanisms via the pre-SMA and the rIFC which may send a command directly to STN and diminish in turn the excitability of M1. The second, indirect pathway, involves the striatum within the fronto-striatal loop. Striatum is hypothesized to mediate the proactive and more selective behavioral inhibition (Aron, 2010). The complex network involved in inhibitory processes is modulated by midbrain dopaminergic neurons in the substantia nigra/ventral tegmental area (SNc/VTA), by brain stern serotonergic neurons in the raphé nuclei and by (to relevant stimuli) time-locked phasic activation of brain stern noradrenergic neurons in the locus coeruleus (LC) (Dalley *et al* 2011).

Neuropharmacology of motor impulsivity

Previous and recent findings implicate dopamine (DA), noradrenaline (NA), serotonin (5-HT), glutamate (Glu), cholinergic and cannabinoid transmission in motor impulsivity (Pattij & Vanderschuren, 2008, Dalley & Roiser 2012, Bari & Robbins 2013). Neuropharmacological studies generated sometimes conflicting results (e.g. concerning DA). This may be caused by the complexity of interacting neurotransmitter systems and their inverted U-curve of action (e.g. DA) (Dalley & Roiser 2012). The difference at the neurochemical level between action restraint (assessed by GNG) and cancellation (assessed by SST) seems to be significant (Eagle *et al* 2008).

DA action changes in function of brain area (Pattij & Vanderschuren 2008) and baseline level (Bari & Robbins 2013). There is no clear evidence about the role of DA in motor impulsivity in the SST or GNG tasks, but DA seems to have an influence rather on go-trials in the GNG task (Eagle *et al* 2008). The main effect of psychostimulants reducing impulsive behavior in ADHD seems to be mediated via NA (Pattij & Vanderschuren 2008). Studies with NA reuptake inhibitors showed that NA neurotransmission changes activity in rIFC and plays an important role mainly in impulsive action (SST) (Eagle *et al* 2008). NA effect is not baseline dependent as it speeds the inhibitory answers in normal humans as well as in ADHD patients (Bari & Robbins 2013). Serotoninergic system seems to play a role only in action withholding (GNG) (Dalley & Roiser 2012), as its prefrontal depletion led to disruption in GNG,

but had no effect on SST (Eagle *et al* 2008). 5-HT may further have a neurotrophic role and a strong impact on other neuromodulator systems and brain connectivity during development. Nevertheless, a non-physiological disbalance (between DA and 5-HT or between DA and NA) may be present in the etiopathogenesis of impulsive symptoms (Dalley & Roiser 2012). An impaired NMDA neurotransmission, mainly in the medial prefrontal cortex (MPFC), is hypothesized to produce impulsive behavior. Furthermore, cannabinoid system (through (CB1) receptors) is involved in response inhibition, because marihuana use provoked impulsive action in the SST and CB1 agonist impaired and antagonist enhanced response inhibition in SST. The endocannabinoid system may play a modulatory role on DA and NMDA systems in the PFC and striatum (Patti & Vanderschuren 2008). The role of cholinergic neurotransmission (nicotinic receptors) in response inhibition is baseline dependent. Their higher activity improved the performance in SST in high-impulsive subjects and ADHD patients, but this effect is considered to be mediated by the positive effect of nicotine on attentional levels. To the drugs which have been shown to impair the SST performance, belong: benzodiazepines, cannabinoids and alcohol (Bari & Robbins 2013). In summary, targeting the NA neurotransmission and NMDA receptors activity seems to be a promissing neuropharmacological treatment possibility for impulsive symptoms (Pattij & Vanderschuren 2008).

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