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A cognitive neuropsychiatric analysis of psychomotor symptoms in major depression and schizophrenia

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Abstract

A cognitive neuropsychiatric analysis will be proposed by presenting recent research on -1-motor control, and -2-action monitoring in two psychiatric disorders i.e. major depression and schizophrenia.

Motor control is best studied from the broader cognitive neuropsychological perspective of action control. Even very simple actions implicate quite diverse brain activities reflecting the cognitive processes of planning, selection, visuomotor integration, timing, force adjustment, and action monitoring. The extent to which deficits in these cognitive processes cause slowed or stereotypic actions can be experimentally studied in clinical settings by means of graphic tasks, as will be illustrated.

A central process in motor/action control is error monitoring. The last decade research on this higher cognitive control process has been booming, also because the detection of errors is accompanied by a clear peak in the EEG, known as the error-related negativity (ERN). Deficient error monitoring has been observed in several psychiatric disorders. ERN studies in major depression and schizophrenia will be discussed.

Psychiatric disorders can best be understood by considering three perspectives, i.e. psychopathology, cognitive neuropsychology and neuroscience. The findings support the view that cognitive neuropsychiatry should involve the combined study of psychiatric symptoms, cognitive dimensions and neurological structures.

Key words: Cognitive neuropsychiatry; major depression; schizophrenia; psychomotor; action monitoring.

The current descriptive syndrome classifications, DSM-IV and ICD-10, have no empirical basis as models of normal cognitive processes. Therefore the traditional psychiatry and neurology have only limited possibilities to explain the cognitive processes underlying the various neuropsychiatric conditions. In scientific perspective this means that the gap between clinical psychiatry, based on syndrome classification, and epidemiology, genetics and neuroscience is often too large to offer clinical explanations of psychopathological phenomena.

Cognitive neuropsychiatry (CNP) attempts to bridge this gap by combining the fields of (a) psychopathology, (b) cognitive neuropsychology and (c) neuroscience and explains clinical psychopathologies in terms of deficits of normal cognitive mechanisms and underlying brain structures (1): (a) Psychopathology is a partly descriptive science of psychiatric illnesses, of the suffering or of the actions or experiences that can be a sign of psychic illness. Psychopathology forms the basis of therapies such as psychotherapy. (b) Cognitive neuropsychology encompasses the study of patterns of cognitive impairments shown by brain-damaged patients in order to provide valuable information about normal human cognition. And finally (c) cognitive neuroscience uses numerous brain-imaging techniques to study aspects of brain functioning and the structures relevant to human cognition.

In the multidisciplinary approach of CNP, the phenomenological manifestations i.e. specific symptoms of disorders, rather than the syndrome as a whole are the starting point. First, the functional organisation of psychiatric disorders is established within a framework of human cognitive neuropsychology and second this framework is linked to relevant brain structures and their pathology. In this way cognitive neuropsychiatry seeks to understand the cognitive processes underlying psychiatric phenomena and ultimately tries to relate these processes to brain functions and brain anatomy (2). The convergence between the cognitive neurosciences and clinical psychiatry provides a cognitive platform from which the various psychiatric conditions can be better understood. Such a platform allows the understanding of psychiatric symptoms in a principled and testable manner.

A design for such a cognitive neuropsychiatry concept will be proposed and discussed in this article. Recent research from our and other research groups on -1- motor control, and -2- error related negativity in two psychiatric disorders i.e. major depression and schizophrenia will be presented. The first paragraph will focus on the cluster of psychomotor symptoms. Starting from a functional model, a reliable and valid method to measure this cluster will be explained and the results of its application in several healthy and clinical populations will be discussed. The results of research in major depression and schizophrenia will be presented more in detail.

The second paragraph focusses on electrophysiological research into these two conditions using an event related potential design, the error related negativity (ERN). An overview of the current knowledge of the mechanisms involved in the ERN and of the results in major depression and schizophrenia leads to a cognitive neuropsychiatric analysis that links symptoms to brain functions and brain anatomy.

From motor control to action control

Processes and brain areas

Even very simple actions like grasping and moving a cup, implicate quite diverse brain activities reflecting the cognitive processes of planning, selection, visuomotor integration, timing, force adjustment and action monitoring. The neurocognitive processes that support motor control in these simple actions, are listed in table 1, which is based on a neuropsychological theory by Willingham (3) and is modified by Ridderinkhof *et al.* (4) and Rushworth *et al.* (5). It is clear that motor control involves more than an adjustment of timing and forcing of muscle innervations. However this list is by no means exhaustive or final for more complex actions, but the model can importantly help us to understand the functional and structural patterns of impairment of motor control in patient populations.

As shown in figure 1 the different functional processes necessary to complete an action can be localized in specific anatomical brain structures.

Experimental studies in clinical settings

The extent to which deficits in cognitive processes cause slowed, impulsive or stereotypic actions can be experimentally studied in clinical settings by means of graphic tasks. Our research group investigates psychomotor symptoms, a broad term to indicate disturbances in planning, initiation and execution of movements. This term is used to describe every activity and every symptom in which movement is the most important component. An important psychomotor dimension in psychiatry is psychomotor retardation, which is a significant – and sometimes even core symptom – of a number of axis I (and axis II) disorders for example in mood disorders (6) and in schizophrenia (7). However it is also an important symptom in normal ageing as well as in many neurological diseases (e.g. morbus Parkinson). In our laboratory, we have developed a technique to measure psychomotor retardation by using a graphic tablet and a pressure-sensitive ballpoint. Stimuli are presented on a monitor placed in front of the participant and the person needs to copy the figure that is presented on the monitor as fast as possible. By obtaining precise measurements of the accuracy and the speed of the execution of this task a complete movement analysis is possible. The following measures can be derived: (1) reaction time (RT), i.e. the time between the presentation of the

Table 1

The neurocognitive processes that support motor control (Modified from Willingham)

Process	Function in Motor Control	Anatomic Locus
Strategic	Goal or action selection	
	Switching to more optimal actions	
	Inhibition of unwanted tendencies	Various regions in frontal cortex
Perceptual motor integration	Selection of spatial targets	Parietal cortex
	Transfer to egocentric space	Premotor cortex
Sequencing	Ordering of movements in the correct sequence	Basal ganglia and supplementary motor cortex
Timing and force control	Adjustment of time and force of movements or muscle commands	Cerebellum
Dynamic	Innervating muscles	Motor cortex
Monitoring	Evaluating outcome	Medial frontal cortex

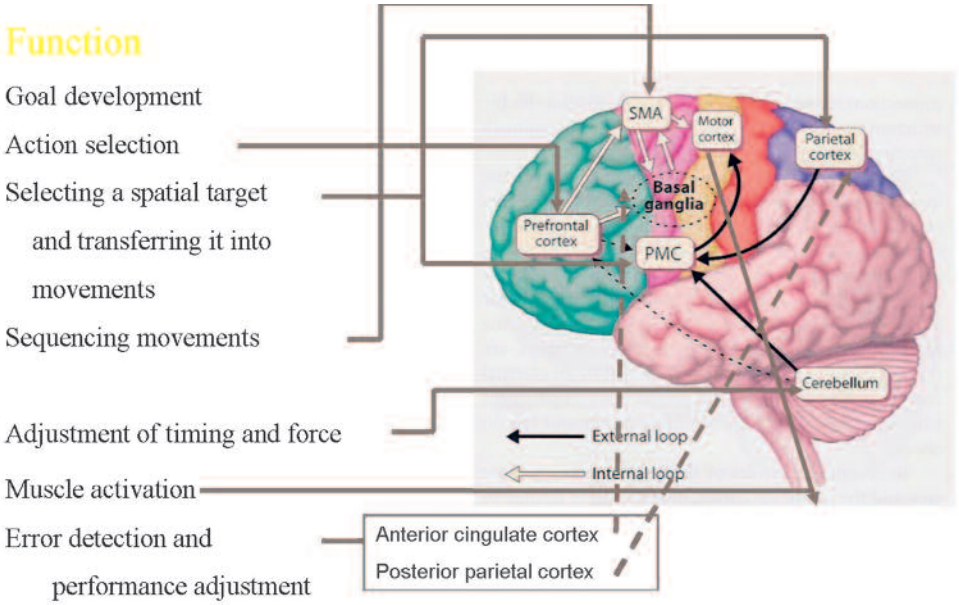

FIG. 1. — Function and anatomical localization in action

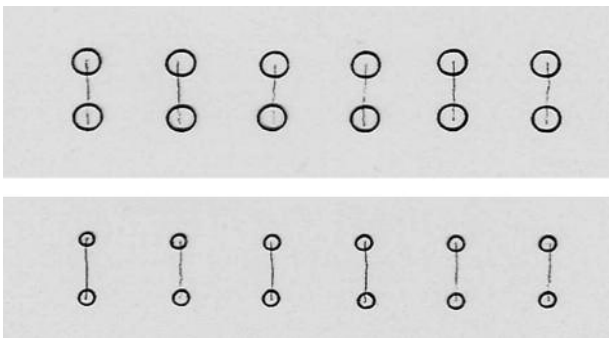

FIG. 2. — Fitt's task: the subject needs to connect the circles (diameter: 0.5 cm or 0.25 cm) by drawing vertical lines of 1 cm.

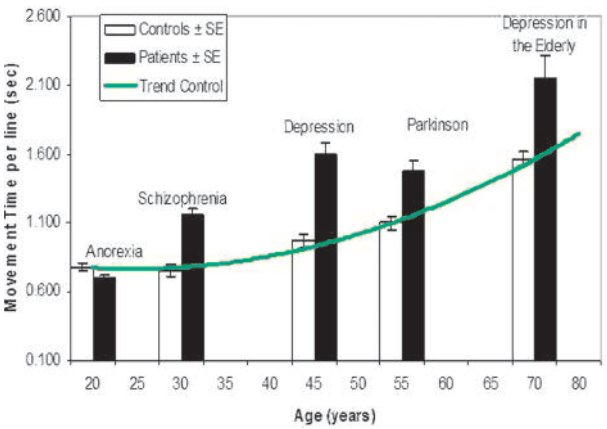

FIG. 3. — Movement times on the Fitt's task and mean age for different subject groups.

stimulus and the start of the first drawing movement, taken to mainly reflect cognitive components and, (2) movement time (MT), i.e. the interval between the start of the first and the completion of the last drawing movement, assumed to mainly reflect the fine motor components. The complexity of this task can vary by using different kinds of figures. A variant of this task is the Fitt's task (8) as presented below (Fig. 2). The person needs to connect the circles by drawing a vertical line between the circles. It is a simple task that is comparable to a simple movement like grasping a glass.

Figure 3 depicts the movement times on the Fitts task for different patient groups. This figure demonstrates that the different groups substantially differ in their movement times on a relatively simple task like this Fitts task. The mean age of each group is depicted on the horizontal axis. As expected, people are much slower at the age of 70 compared to the age group of 20. Interestingly, the group of patients with major depressive disorder (MDD) is considerably slower than the age-matched healthy control group. In addition the MDD patients even have a movement time that is similar to that of patients with Parkinson disease or that of healthy elderly participants (mean age of 70). The main question is whether this slowing has the same cause.

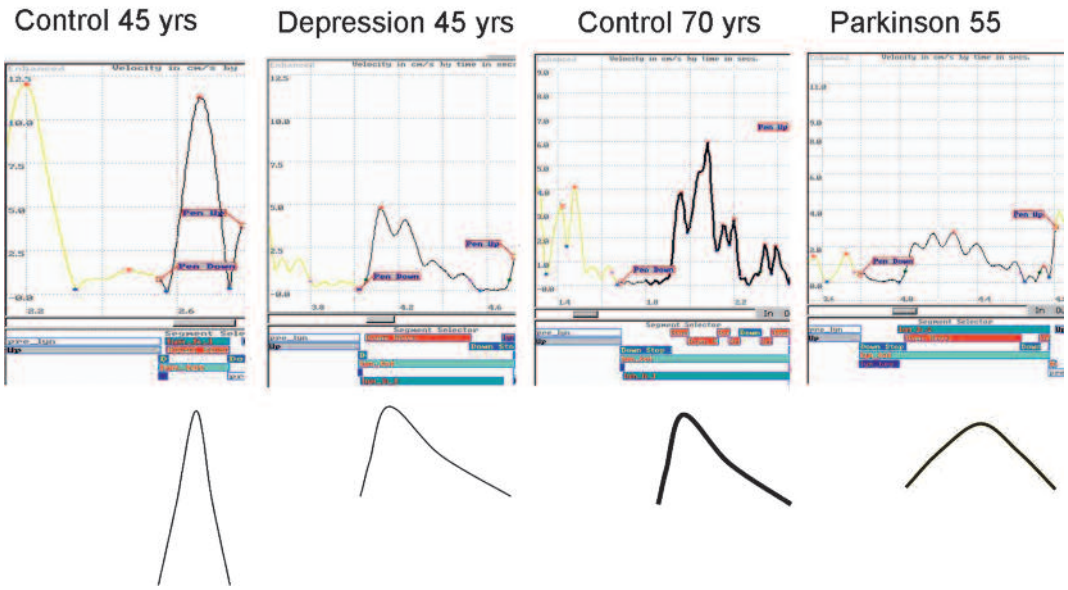

FIG. 4. — Fine movement analysis shows different velocity profiles in different subject groups

The next graphs (Fig. 4) show a fine movement analysis of the mentioned groups. Movement times are measured when patients copy a figure that is presented on a monitor as fast as possible as explained above. Controls of the age of 45 have a bell-shaped velocity profile with one high peak. MDD patients who need much more time, start moving relatively quick but show a lot of velocity differences once approaching the target. Whereas the group of elderly (mean age: 70) shows a similar velocity profile, but with the exception of a higher ballpoint pressure. Patients with Parkinson show a different i.e. more symmetric velocity meaning that the starting time is slower and that there are less differences in velocity. Hence in this experiment we see 3 different velocity profiles in 3 different groups of patients, suggesting dissimilar causes of their kinematics.

As described above psychomotor retardation is a clinical dimension manifested in a number of axis I (and axis II) disorders such as mood disorders, schizophrenia, eating disorders, ageing and morbus Parkinson. Interestingly, the detailed analyses of movement parameters reveal that these manifestations most likely have a different nature.

PSYCHOMOTOR RETARDATION IN DEPRESSION

Even within one single syndrome like depression we find different psychomotor patterns in the different subtypes of depression (9). In the subtype melancholia psychomotor retardation seems to be of great importance, this holds for cognitive slowing as well as for motor slowing. On the other hand retardation could not be demonstrated in the subtype of dysthymia, a less severe type of depression (10).

Interestingly the profile of cognitive disturbances in a related disorder i.c. mania does not differ that much of the profile in depression. Of course in mania there is an additional loss of inhibitory control, but the further profile seems to resemble that of depression. Probably the neurobiological determinants of these two psychiatric disorders have much in common while the clinical presentation is very different (11). In follow-up studies on mood disorders it becomes clear that cognitive disturbances (especially disturbances in the executive functions) partly persist after acute treatment even when the mood disturbances resolve. Furthermore, during the acute treatment (first 6 weeks) there is no evidence that the course of changes in cognitive disturbances differ from the course of changes in mood disturbances (12). Therefore it can be suggested that these two syndromes exist independently.

Explanations of these phenomena are lacking. Therefore it is necessary to combine the clinical features of depression, the cognitive disturbances (especially executive functioning) and the available techniques of neuroscientific research.

PLANNING DEFICITS IN SCHIZOPHRENIA

Psychomotor slowing is considered an important clinical phenomenon in schizophrenia but its exact nature remains unclear as it involves multiple aspects

such as goal selection, inhibition, planning, sequencing and execution. It is an important symptom since psychomotor slowing is a prognostic factor for poor social, functional and clinical outcome (13).

Planning is part of executive functioning. The most important executive functions are the planning of goal directed actions, reacting in a flexible manner to changes, controlling the attention and choosing a good strategy. In the following lines we use the term 'planning' but mean this to refer to a number of processing activities that for the most part evolve in the initiation stages of a movement sequence.

In order to study planning processes and perseveration during fast motor actions, a new drawing task is developed requiring subjects to connect pairs of small open circles with straight lines in sequences of ten pairs. This line-sequencing task consists of five trials in which the sequence of line orientation 'rises' from horizontal to vertical (Sequence 1) and of five trials in which the line orientation 'drops' form vertical to horizontal (Sequence 2). These trials alternate in random order with control trials with a random sequence of line orientations. Perseveration in this task was operationalized by the percentage of trials executed without switches. Vertical lines are most frequently drawn from top to bottom and horizontal lines from left to right. If, in a sequence of lines, the line orientation changes progressively in small steps, then at some line tilt the subject has to resolve the conflict between these two preferences and must 'switch' from one to the other. Results are shown below (Fig. 5).

All schizophrenia patients were recently diagnosed with a schizophrenia-spectrum disorder (schizophrenia, schizoaffective disorder or schizophreniform disorder), based on a structured clinical interview for DSM-IV (SCID-I). At the time of testing all patients were medication-free.

According to the results schizophrenic patients more often opted for the uncomfortable bottom-up direction to draw the vertical lines and changed their orientation less often than the controls did, which could be explained by the perseveration schizophrenic patients show. In the control sequences the drawing directions were quite similar to those of sequence 1. So it seems that patients avoid to make the decision which drawing direction to choose. They choose only one strategy and draw all lines from left to right or from bottom to top. This however is at the cost of drawing precision as we see that schizophrenic patients have a larger number of overshoots. These results indicate that recent-onset schizophrenic patients have impairments in the coherent planning of simple motor sequences even before slowing is becoming evident.

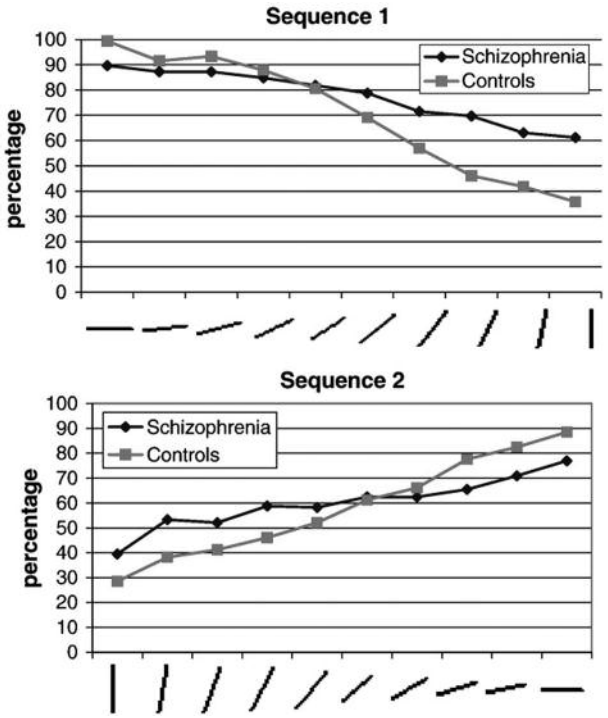

FIG. 5. — Line sequencing task. Percentages of lines drawn starting from the bottom left in Sequence 1 (top graph) and those drawn starting from the top right in Sequence 2 (bottom graph) by Grootens *et al.*

To summarize, the psychomotor findings in patients with schizophrenia and major depression clearly support the implication of cognitive neuropsychology for psychiatric and neurological diseases. Two important symptoms i.e. psychomotor retardation and planning deficits can be measured in a valid and reliable way. The patterns of these impairments differ in one syndrome, between several syndromes, and in comparison with healthy persons even before clinical impairments are manifest. Detailed investigation into one symptom domain gives the opportunity to differentiate different subtypes in one syndrome, as it is shown in the example of major depression. On the other hand it is possible to distinguish between healthy and non-healthy subjects even before overt clinical symptoms manifest themselves as it is shown in the example of planning deficits in schizophrenia.

Action monitoring

A central process in motor/action control is action or performance monitoring i.e. the continuous evaluation and adjustment of an ongoing action. During the last decade research on this higher cognitive control process has been booming. The detection of

errors in speeded choice-reaction tasks is accompanied by a clear negative peak in the EEG, known as the error-related negativity (ERN). The ERN peaks within a 100 msec after the onset of the erroneous response. Several studies, applying different localisation techniques and functional imaging, have identified posterior medial frontal cortex (pMFC), including anterior cingulate cortex (ACC) and pre-SMA, as the neural generator of the ERN (14). Coles *et al.* (15) proposed the so-called Mismatch Theory of the ERN that explains the functional processes resulting in the generation of the ERN. This theory was later extended by Holroyd and Coles (16) into the reinforcement-learning theory of the ERN. According to these models, the error-detection mechanism is comprised of two components i.e. a monitoring system that detects errors and a behavioral adaptation system. Pivotal to this system is the so-called comparator. When a motor command is issued, a representation of the actual response arrives at the monitoring system and is compared with the representation of the goal response. When the actual events are better than expected a phasic increase in the activity of the dopamine system is induced, and when the events are worse than expected a phasic decrease in dopaminergic activity is induced. The ERN is generated when a phasic decrease in dopaminergic activity disinhibits the apical dendrites of neurons in the ACC. Importantly, the ERN functions as input for the behavioural adaptation system by optimizing the filtering function of the ACC in order to select appropriate motor controllers.

A common used speeded choice-reaction task to provoke errors is an Eriksen Flankers task (17). Subjects are shown a congruent (SSSSS or HHHHH) or incongruent (SSHSS or HHSHH) letter string and consecutively they need to responds as fast as possible by pressing a button with either their left or their right index finger depending on whether the central letter is an S or an H. When, for example, the letters SSHSS are shown, the goal response is to press a button with the right index finger. However, under time pressure subjects are more likely to make errors (make a left button press) because of the incongruent letters flanking the central target letter. In the case of an error, the comparison of the actual and the goal response will result in a mismatch. Because this event is worse than expected a phasic decrease in dopaminergic activity is induced and an ERN is generated in the ACC. This ERN is used as input for the behavioural adaptation system so that the person can prevent similar errors in the next trials. Slowing down after an error is an example of an adequate behavioural adjustment in a speeded choice-reaction task like the Flankers. This behavioural adaptation is known as post-error slowing, first reported by Rabbitt (18). Post-error slowing is interpreted as an involuntary and cautionary response strategy which is part of an early automatic adaptive process.

Indirect evidence for the involvement of dopamine in error monitoring comes from patient studies. Patients diagnosed with diseases in which dopamine plays a key role such as Parkinson's disease (19) and Huntington's disease (20), show altered ERN, Holroyd *et al.* however couldn't find any ERN disturbances in patients with mild to moderate Parkinson disease (21). More direct evidence comes from studies using pharmacological manipulations in healthy volunteers. De Bruijn *et al.* conducted two studies in which ERN amplitudes were measured in a group of healthy volunteers after administration of D-amphetamine (15 mg), Lorazepam (2.5 mg), Haloperidol (2.5 mg), Olanzapine (10 mg), and Paroxetine (20 mg) (22).

D-amphetamine is a stimulant and an indirect dopamine agonist as it releases dopamine from presynaptic dopamine terminals and increases the dopamine levels at the postsynaptic receptors and it is known to stimulate the ACC, caudate nucleus, putamen, and thalamus.

Lorazepam is a benzodizepine with sedative characteristics caused by GABA-ergic pathways that directly innervate the ACC.

Haloperidol and Olanzapine are dopamine receptor antagonists and Paroxetine (20 mg) is a selective serotonin reuptake inhibitor without dopaminergic activity (23). In line with the presumed role of dopamine in the reinforcement-learning theory, these studies showed that ERN amplitude increased after administration of D-amphetamine, while administration of Haloperidol decreased ERN amplitude. Suppression of action monitoring, as reflected in reduced ERNs by lorazepam is explained by the GABA-ergic activity in the ACC and the resulting sedative side effects. The same was also found after administration of Olanzapine. Finally, paroxetine did not affect ERN amplitudes, suggesting that either serotonin is not directly involved in action monitoring, or that increasing serotonin levels through a single-dose administration in healthy volunteers is not effective. In sum, these findings from psychopharmacological studies in healthy volunteers provide evidence for the involvement of dopamine in action monitoring.

Major depression and schizophrenia

Deficient action monitoring has also been observed in several psychiatric disorders. The ERN disturbances in the two psychiatric disorders major depression and schizophrenia, can partly be

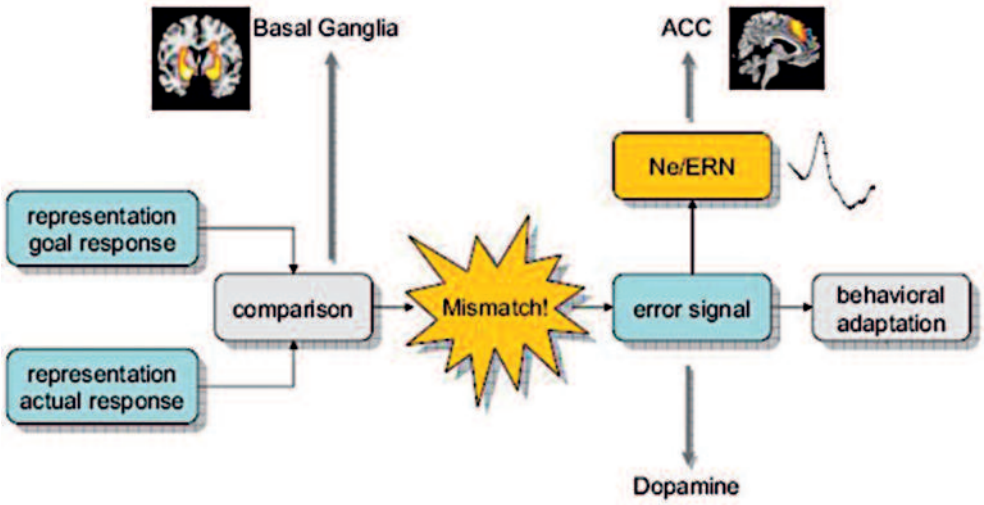

FIG. 6. — Mismatch theory by Holroyd and Coles

explained by the central role of dopamine in these pathologies. Moreover several findings show a relationship between the disturbances in action monitoring and psychomotor symptoms that are also associated with dopaminergic disturbances.

For schizophrenia Bates *et al.* (24), for example, reported an association between clinical evaluated psychomotor poverty and diminished ERN amplitudes. For major depression a recent study showed correlations between diminished ERN amplitude and psychomotor slowing in severely depressed (25) patients. On the other hand two studies (26) with moderately depressed patients without psychomotor slowing showed enhanced ERNs.

Regions that are involved in psychomotor symptoms in these disorders are dorsolateral prefrontal cortex (DLPFC), angular gyrus, ACC and supraorbital frontal areas with striatal dopaminergic dysfunction playing a substantial role (27). The DLPFC, basal ganglia, supplementary motor area (SMA) and ACC are assumed to regulate the preparatory processes of a movement. As these regions overlap with the neural substrates of action monitoring and as dopamine plays a crucial role in both processes, we assume that action monitoring forms an integral part of the complex interactive network of processes involved in the preparation and execution of a motor act (28).

Conclusion

To this date, the traditional extensive phenomenological and descriptive exploration of symptoms in psychiatric syndromes have not led to sufficient knowledge of the pathogenesis of these syndromes. However the new approach of cognitive neuropsychiatry creates the opportunity to develop pathogenetic research as illustrated above in major depression and schizophrenia. In these examples exhaustive observation of the cluster of psychomotor symptoms at a clinical level and the combined use of multimodal technologies (experimental cognitive tasks and electrophysiological tasks) might lead to a cognitive model underlying the clinical symptoms. This modelling provides a better insight in the psychopathology and pathogenesis of symptoms and allows to link these symptoms to different frontostriatal dopaminergic dysfunctions. In this way a neurocognitive analysis makes it possible to '*move beyond diagnosis and classification, toward offering a cognitive explanation for the disorder and, as an important second, location of the brain system*' (29). Whereas it is often assumed that psychomotor symptoms originate from one general syndrome, reflecting a similar pathophysiology (30), cognitive neuropsychiatry of these symptoms in schizophrenia and major depression point to different pathogenetic mechanisms and to the existence of different diagnostic subgroups. Therefore cognitive neuropsychiatry not only provides the opportunity to develop a broader look over the borders of existing syndrome classifications but could also contribute to better treatment schemes. In major depression for example the dopamine hypothesis could lead to a stronger focus on dopaminergic agents in the subgroup of MDD with psychomotor retardation.

Finally in practice CNP demands an intensive cooperation between the clinical psychiatrist and the

cognitive psychologist. This tandem should be assisted by specialists from other disciplines like (neuro)imaging, epidemiology, genetics, and fundamental neuroscience. Both the clinical psychiatrist and the cognitive psychologist need to identify the symptoms and clinical dimensions that are useful for cognitive analysis and need to deliver tasks and test settings which make it possible to come to an analysis. The resulting neurocognitive analysis then needs to be tested back in clinical practice leading to a better understanding of the psychopathology (31).

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