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RESEARCH PROJECTS IN THE COLLABORATIVE ANTWERP PSYCHIATRIC RESEARCH INSTITUTE

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SUMMARY

Introduction: *In the following article CAPRI presents its current research projects.*

Subjects and method: *The team leaders were asked to present and summarize the project they had been working on. The fields in which research was conducted are: Child and Adolescent Psychiatry, Cognitive and Psychomotor Dysfunctions in Schizophrenia, fMRI in Schizophrenia, Cognitive and Psychomotor Dysfunctions in Major Depressive Disorder, Chronic Fatigue Syndrome, Addiction Medicine and Forensic Psychiatry.*

Results: *An overview of recent and ongoing research projects is provided and the main results are summarized.*

Key words: *child and youth psychiatry – schizophrenia – fMRI - major depressive disorder - chronic fatigue syndrome – addiction - forensic psychiatry*

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INTRODUCTION

The Collaborative Antwerp Psychiatric Research Institute (CAPRI) is a scientific research centre of (neuro-)psychiatry and mental health. Research takes place in the field of adult as well as child- and adolescent psychiatry at the University of Antwerp, Faculty of Medicine.

This refers to all activities of research concerning clinical psychiatry and clinical psychology focused on psychiatric disorders in children, adults and the eldery. We conduct scientific research in the distinct fields of (neuro-) psychiatry at the University of Antwerp, the University Hospital Antwerp (UZA; Universitair Ziekenhuis Antwerpen) Department Psychiatry, the UCKJA (Universitair Centrum Kinder- en Jeugdpsychiatrie/AZ Middelheim te Antwerpen), the General Centre Hospital Antwerp (Algemeen Centrumziekenhuis Antwerpen)-Campus Stuivenberg and the Psychiatric Hospital St-Norbertushuis (Duffel).

The purpose of this scientific research is to understand the basics that are responsible for specific psychiatric disorders, in order to improve diagnostics and treatment. This research is executed from different angles, e.g. epidemiology, genetics, cognitive neuroscience, neuro-imaging, experimental psychopathology and psychoneuropharmacology.

In the following article the current projects will be briefly presented and summarized.

METHOD

Ongoing research domains are: Child and Adolescent Psychiatry, Cognitive and Psychomotor Dysfunctions in Schizophrenia, fMRI in Schizophrenia, Cognitive and Psychomotor Dysfunctions in Major Depressive Disorder, Chronic Fatigue Syndrome, Addiction, and Forensic Psychiatry. The different team leaders were asked to present their own research projects. This resulted in a complete overview of our scientific activities.

RESULTS

Child and Adolescent Psychiatry

The CAPRI department Youth Mental Health contributes in the research into the aetiology of disturbances and psychopathology in the development of children and adolescents. Other fields of interest are the relation between psychopathology and delinquent behaviour in adolescents, and the efficacy of care and treatment for children and adolescents.

Research into the domain of the aetiology of disturbances in development focuses on the relation between prematurity and developmental disturbances (Janssens et al. 2009) and on the neurobiological and molecular genetic correlates of psychopathology, more specific Autism Spectrum Disorders and Conduct

Disorders (Croonenberghs et al. 2007; Croonenberghs et al. 2008; Van West et al. 2009a; Van West et al. 2009b; van West et al. 2010; Simons et al. 2006). At this moment we conduct research on the differences in neuropsychological functioning and stress coping (HPA-axis) between proactive and reactive aggressive adolescents.

In the domain of developmental epidemiology and the relation between psychopathology and delinquent behaviour many research has been done in collaboration with the University of Amsterdam and Yale University. This research was and still is in many ways the basis for the development of the Belgian child and adolescent forensic psychiatric care (Vermeiren 2004a; Vermeiren 2004b).

The third area of research concerns the efficacy of care and treatment for children and adolescents and the determination of the factors that influence this efficacy. It is generally accepted that for many children and adolescents, who suffer from psychopathology, collaboration between different care systems, services or professionals is necessary to fully meet their developmental needs. Making this a reality, however, is quite difficult. Based on a participatory action research approach different research projects are carried out in the domain of organization, collaboration, wraparound and evaluation of child and adolescent mental health care (Janssens & Deboutte 2009; A. Janssens & Deboutte 2010; Janssens et al. 2010). At the same time a system for monitoring regular and specialist child and adolescent care and treatment is build up and is being evaluated in close collaboration with ZNA University Centre Child and Adolescent Psychiatry Antwerp.

It is well established that parents and parenting are important in the prevention and treatment of psychopathology of children and adolescents. The Triple P system of parenting support is one of the most cost effective population based programs in this field (Sanders 2008). At this moment the program is implemented and evaluated at a population level in the province of Antwerp. Different trials are carried out for parents with intellectual disabilities or psychopathology (addiction, psychosis) (Glazemakers & Deboutte 2010).

Cognitive and Psychomotor Dysfunctions in Schizophrenia

Classically, symptomatology in schizophrenia is subdivided in three symptom groups: the positive, negative and cognitive symptom domain. However, an additional group of psychomotor symptoms can be observed in the illness. Psychomotor symptoms are those symptoms in which, rather than thinking or feeling, movement or action is the principal component, i.e., in which the planning, programming, and execution of movements play a dominant role. These symptoms can be classified into three main groups. Patients may exhibit psychomotor slowing, catatonic symptoms and neurological soft signs (NSS). Catatonic symptoms are specific motor abnormalities, such as stereotypy (Morrens et al. 2006a), stupor or mutism. Psychomotor slowing (PS) i.e. slowing in the planning and execution of movements can also be observed in schizophrenic patients. NSS include deficits in motor coordination, motor sequencing and sensory integration.

Since the last decade, a revival of interest in cognitive and, to a lesser extent, psychomotor symptoms can be observed (Morrens et al. 2008b). This results from an increasing body of evidence that shows that these two symptom domains are, in contrast with positive symptoms, related to clinical, social and functional outcome in patients (Morrens et al. 2008b).

The prevalence of psychomotor symptoms in schizophrenic patients

Recent research has found that catatonic features are as prevalent now as they were in the preneuroleptica era. Cohort studies demonstrate that 21-33% of schizophrenic patients display catatonic symptoms which is similar to the prevalence of 30% described in the preneuroleptic era.

Similarly, the prevalence of the presence of at least one neurological soft sign in schizophrenic patients NSS is 88-100% whereas this is only 0 to 5% in healthy controls, making these highly common symptoms in the illness.

Finally, psychomotor slowing has systematically been shown to be present in schizophrenic patients (Morrens et al. 2007). A recent study demonstrated that psychomotor speed is much more affected than classical cognitive domains in the illness (Morrens et al. 2008c).

It can be concluded that these symptoms are still highly prevalent; and Fink and Taylor (Fink & Taylor 2001) argue that the reports of diminished occurrence of these symptoms partly result from the fact that the contemporary clinician lacks attention and focus towards these symptoms.

Cognitive versus psychomotor symptoms

Some psychomotor symptoms are often mistakenly held to be symptoms that are more cognitive in nature. This is comprehensible, since a strict distinction between motor activities and higher mental activities is impossible. We can only become aware of a cognitive activity through motor output, however small. Conversely, all motor actions need at least a few rudimentary higher-order activities of goal selection and planning, and these are hardly possible without perception.

Psychomotor slowing versus processing speed

Nevertheless, psychomotor slowing has often been confused with reduced processing speed, a cognitive symptom. In order to investigate the distinction between these two symptoms, we performed a series of studies.

Our group (Morrens et al. 2006a) investigated whether psychomotor slowing can be divided into

distinct processes that differentially affect cognitive functioning in schizophrenia. The pen-tip movements of 30 schizophrenic inpatients and 30 matched controls were digitally recorded during performance of the Symbol Digit Substitution Test (SDST), a commonly used task to assess psychomotor slowing, and analysed to differentiate matching time and writing time, representing the cognitive and sensorimotor component of slowing, respectively. In addition, the results were compared to each other and to the scores of traditional neuropsychological tests that assess domains such as memory and attention. Both matching time and writing time were longer in the schizophrenic patients relative to the controls but did not correlate. Only matching time correlated significantly with the conventional neuropsychological test results. These findings imply that, although schizophrenic patients display both sensorimotor and cognitive slowing, the two processes are unrelated. Furthermore, only the cognitive component of slowing was associated with most of the cognitive deficits as measured by traditional neuropsychological tests. So, even if the SDST is widely used to assess psychomotor speed, the task also taps several higher-order cognitive processes and is probably not the best tool to assess psychomotor slowing.

Therefore, in a follow-up study, we recorded the motor performance on a series of copying tasks using a digitizing tablet allowing a more precise measurement of the aforementioned psychomotor processes and the investigation of any subprocesses in a sample of schizophrenic patients. The copying tasks were found to grasp psychomotor slowing more properly, whereas the SDST was shown to be a more appropriate tool to assess processing speed (Morrens et al. 2008a).

Stereotypy versus perseveration

Analogous to the confusion between psychomotor slowing and processing speed, two other symptoms have not been properly delineated. Stereotypy is a symptom characterized by repetitive, functionless motor behaviour. Perseveration is also a symptom that is characterized by repetitive behaviour, but is more cognitive in nature. Whereas cognitive dysfunctioning is known to remain stable throughout the illness, less is known about the course of the motor symptoms.

The Zeigeversuch (Mittenecker 1953), which entails the generation of a random sequence of button presses, was claimed to capture stereotypy. We used a newly designed computerized version of the Zeigeversuch, the Stereotypy Test Apparatus (STA) to evaluate the evolution of stereotypy during the course of the illness. To assess stereotyped and perseverative behaviour 58 schizophrenic inpatients and 48 healthy controls performed the STA and the Wisconsin Card Sorting Test (WCST), respectively, as well as several other traditional neuropsychological tests and the Symbol Digit Substitution Test (SDST) on a writing digitizer (Morrens et al. 2006b). The STA correlated only weakly with the WCST and SDST measures but not with the cognitive or motor slowing on the SDST, nor with the other cognitive measures. Stereotyped and perseverative idiosyncrasies both seem to increase in the course of the illness, in contrast with other cognitive dysfunctions. However, the increase in stereotypy was found to be a specific effect of the illness, whereas the subtle increase of perseverative responses was a general aging effect that is also found in healthy controls. In addition, perseveration is already present in the early stages of the illness, while stereotyped behaviour only manifests itself in the later stages of schizophrenia. Our results may also suggest that in schizophrenia catatonic symptoms like stereotypy are present subclinically and may even be part of the natural course of the illness. Accordingly, stereotypy could be delineated from perseveration, thus demonstrating once again differences between cognitive and motor processes.

Evolution through the illness of psychomotor and cognitive symptoms

Initially, in the early course of the illness, there is a worsening of the already present cognitive deficits. This initial drop in cognitive functioning is thought to take place around the period of the first psychotic episode. Afterwards, these symptoms remain stable throughout the illness.

Psychomotor symptoms on the other hand seem to worsen through the illness. We demonstrated (Morrens et al. 2006b; Morrens et al. 2008b) that stereotypy and psychomotor slowing both seem to increase in the course of the illness in chronically ill, in contrast with the stabilized cognitive dysfunctions. Similarly, Gold et al. (Gold et al. 1999) demonstrated in a longitudinal study that a group of recent-onset schizophrenic patients exhibited stable or improved performance on all cognitive tasks, but that psychomotor slowing was highly significantly worsened at the 5-year follow-up. Chen et al. (Chen et al. 2000) also found that NSS worsened over a period of 3 years in a group of chronic, stabilized patients.

The differential effects of antipsychotics on psychomotor slowing versus higher-order cognitive domains

One of the reasons that may have lead to a reduced interest in psychomotor symptoms is that some authors suggested that rather than an intrinsic feature of schizophrenia, psychomotor symptoms such as slowing are merely a side effect of neuroleptic treatment. Yet, although many studies have tried to implicate anti-psychotic treatment in the generation of psychomotor slowing, the symptom has been demonstrated inde-pendent of medication (Morrens et al. 2007) and was observed and described long before neuroleptics were discovered. Although it was found that conventional neuroleptics do not seem to further slow motor speed, they do not seem to improve the symptom either, whereas atypical antipsychotics do seem to have some

improving effects on psychomotor speed. In contrast both conventional and atypical agents seem to have similar modest improving effects on cognitive functioning in schizophrenic patients (Woodward et al. 2005).

Our group performed a study with cross-sectional design, in which schizophrenic inpatients treated with risperidone (n=26), olanzapine (n=24), other atypicals (n=25) or conventional neuroleptics (n=21), were compared to each other on a series of classical cognitive measures as well as several psychomotor tasks, assessing both psychomotor slowing and stereotypy. The patients on conventional neuroleptics performed worse than the patient group on atypical agents on most of the psychomotor measures for both stereotypy and psychomotor slowing, which difference was not found on the measures for verbal memory, attention, working memory, executive functioning or, importantly, processing speed (Morrens et al. 2008a).

fMRI in Schizophrenia

Recently, a series of five fMRI studies were carried out aimed primarily at developing paradigms for measuring clinically relevant brain dysfunctions in patients with schizophrenia. We identified a number of desirable characteristics for such measurements. First, tests should be selective and sensitive to the disorder. Second, they should focus on cognitive disturbances known to be clinically relevant from behavioural studies. Third, differences in brain activation should be relatable to cognitive processes at a clinically relevant level of description.

The first study (Caulo et al. 2005) is a case study providing evidence that the mammilo-thalamic lesions in Wernicke-Korsakoff syndrome cause a network-level disturbance, resulting in a dysfunction of the temporal lobe. Thus, a functional disruptance of the memory network underlies anterograde amnesia in this syndrome. The second study reports a disruption of a frontoparietal network in schizophrenia. Both frontal and parietal group differences are shown to be closely related to the difficulty of the attentional task used in the study. The problem of task difficulty in interpreting differences between patients and controls was the focus of the third study (Van Hecke et al. 2010). A highly simple working memory task, in which maintenance and manipulation of information could nevertheless be distinguished, was developed. Tests of its ability to evoke relevant activation in control subjects are presented. Study 4 continues the theme of dealing with task difficulty together with the need to tax working memory functions. A continuously-taxing but subjectively simple and error-free spatio-temporal estimation task was developed to reduce performance-related confounds while still evoking strong working memory related activation relevant to psychiatric and neurological disturbances. Tests of task activation and behavioural results in controls are presented. Finally, in the fifth study the estimation task is used in a between group design with schizophrenia patients and controls. The results point to a fundamental disturbance related to the Default Mode Network (DMN) in patients. This network is associated with self-related processes, which may be independent from and even to an extent opposed to the performance of "arbitrary" cognitive tasks. Deactivation of this network predicts performance in behavioural tasks measuring cognitive speed. The most consistent difference between patients and controls was found to be a reduction in DMN deactivation under working memory taxation.

Cognitive and Psychomotor Dysfunctions in Major Depressive Disorder

Major depressive disorder (MDD) is one of the most widespread psychiatric illnesses. Besides depressive cognitions, psychomotor changes and especially psychomotor retardation are core clinical features of an ongoing depressive episode. The work conducted by our research group in the domain of MDD focused on the integrity and significance of both the psychomotor and the action-monitoring process in MDD as both processes are indispensable for an appropriate performance of simple, everyday activities as well as less frequent, more complex actions.

Psychomotor symptoms in MDD

First, our research aimed to more carefully define the psychomotor retardation (PR) seen in MDD patients, and to further investigate the importance of these symptoms in the diagnosis and treatment of MDD. For these studies, a method was developed that allows the psychomotor phenomena to be measured objectively (Hulstijn et al. 2002). This method encompasses drawing tasks in which lines and figures that were presented on a computer screen needed to be copied as quickly and as accurately as possible on an electronic digitizer. Using a specially designed electronic pen, the digitizer and a PC, we were able to record all kinematic aspects of the drawing movements under investigation with a high degree of accuracy. The kinematic data included reaction or initiation time and movement time, reflecting cognitive and motor component respectively. The cognitive component is assumed to mainly encompass the processes responsible for the planning of the movement, while the motor component mainly entails the actual execution of the movement. The studies in which the nature of the slowing was specified in medicated as well as unmedicated depressed patients have shown that MDD patients show a marked psychomotor retardation on all tasks (Pier et al. 2006; Sabbe et al. 1996a; B. Sabbe et al. 1996b; Sabbe et al. 1997; Sabbe et al. 1999; Van Hoof et al. 1998). This PR was found to be cognitive and motor in nature. One of our studies into the psychomotor effects of pharmacological treatment revealed that after treatment with fluoxetine the cognitive slowing had disappeared

whereas the motor slowing persisted. Especially patients with pronounced PR showed the best response to fluoxetine (Sabbe et al. 1996b, Sabbe et al. 1997).

Subsequently, the psychomotor effects of a six-week treatment with sertraline, i.e. an SSRI with additional dopaminergic properties, were investigated in a sample of MDD patients: beneficial effects for sertraline, especially on the lower-order cognitive and motor components were observed (Schrijvers et al. 2009b). Our comparative research of depressive subtypes revealed that, contrary to MDD patients, the psychomotor performance of patients with dysthymia was not impaired (Pier et al. 2004b). Moreover, the presence of PR proved highly relevant for the diagnosis of the melancholic subtype (Pier et al. 2004a). In elderly depressed patients, aging lead to an additive deteriorating effect on their psychomotor performance (Pier et al. 2004c). Additionally, the degree and pattern of psychomotor retardation in MDD was compared with its manifestation in chronic fatigue syndrome (CFS). The pattern of retardation proved slightly different for the two patient groups: although both groups showed similar cognitive impairments, the motor component of the drawing movement was more affected in the MDD patients than it was in the CFS patients (Destoop et al. 2010; Schrijvers et al. 2009b). An overview of the current knowledge on psychomotor symptoms in depression clearly confirmed the therapeutic, pathophysiological and diagnostic value of this symptom profile, and stressed the need for further research in this field (Sabbe 1997; Schrijvers et al. 2008).

Action monitoring and error-related negativity in MDD

Second, a research project was initiated to investigate the integrity of the action monitoring process in MDD. A well-known marker for action monitoring is the error negativity (Ne) or error-related negativity (ERN), an event-related potential (ERP) generated in the anterior cingulate cortex following erroneous responses. The error positivity (Pe) is another ERP associated with the commission of an error. Both types of error-related potentials are typically evoked during the performance of an Eriksen flankers task, a speeded-two choice reaction task that forces participants to make errors. The well-documented knowledge on the neural substrates of the Ne/ERN allows a reliable assessment of the integrity of the action-monitoring process and of ACC functioning by means of electrophysiological recordings of brain activity during the production of errors. Besides the ERP amplitudes, other outcome variables of interest in the flankers task are the various behavioural performance indices, i.e. reaction times and proportions of correct and incorrect responses.

Action-monitoring research is increasingly being applied to the study of psychiatric disorders, such as schizophrenia, obsessive-compulsive disorder, anorexia nervosa, borderline personality disorder et al. (for review: see (Ullsperger 2006). A few years ago, knowledge on the action-monitoring process in MDD was limited. Ne/ERN amplitudes had been investigated in moderately depressed patients only, in general revealing enhanced amplitudes in these samples. Our group was the first to investigate action monitoring in severely depressed patients: whereas, unexpectedly, no group differences (MDD patients vs. healthy controls) could be demonstrated for the Ne/ERN amplitudes, significant between-group differences were found for the error positivity (Pe; Schrijvers et al. 2008). Moreover, the significant and strong correlations between the mean Ne/ERN amplitudes and the patients' psychomotor performance indicated that only severely depressed patients manifesting pronounced psychomotor retardation demonstrate impeded action monitoring (Schrijvers et al. 2008). In a subsequent action-monitoring study we aimed to explore the impact of symptom-severity reduction on the action-monitoring process in MDD. Whereas no improvements could be observed between the assessment at baseline and 7 weeks later, neither for the Ne/ERN nor for the Pe.,a clear association was found between the level of depressive symptom reduction and the level of improvement in Ne/ERN (but not Pe) amplitudes (Schrijvers et al. 2009c). In a final action monitoring study, several perfectionism features appeared to substantially affect Ne/ERN and Pe amplitudes in a sample of depressed patients (Schrijvers et al. 2010).

Chronic Fatigue Syndrome

Introduction

The CAPRI-research projects in the domain of consultation and liaison psychiatry have mainly been focused on chronic fatigue syndrome (CFS), a condition that is characterized by unexplained, profound disabling and long-lasting fatigue that is of new or definite onset, that is not the result of ongoing exertion and that is not substantially alleviated by rest. The fatigue must be accompanied by at least 4 or more of the following case defining symptoms during at least 6 months of consecutive illness: sore throat, tender cervical or Axillary lymph nodes, muscle pain, multi-joint pain, postexertional malaise, un-refreshing sleep, headaches and impaired memory or concentration.

Although several etiological factors have been identified, the underlying pathophysiology of CFS remains unclear (Prins et al. 2006). In this section, we will elaborate on the following three research topics: psychomotor disturbances, neuro-endocrine dysfunction and genetic vulnerability.

Psychomotor disturbances

The majority of patients with CFS complain of deficiencies in attention, concentration and memory abilities. Although in general, neuropsychological studies have produced inconsistent results, slowed processing speed, impaired working memory and poor

learning of information are prominent features of cognitive dysfunction in CFS (Michiels & Cluydts 2001). As to psychomotor functioning, several earlier studies reported prolonged simple or choice reaction times, while others failed to find such delays (Destoop et al. 2010).

Recently, we compared psychomotor function between 38 well-diagnosed CFS patients, 32 major depressive disorder patients and 38 healthy controls by means of computerized copying tasks differing in complexity (Schrijvers et al. 2009a). Both patient groups demonstrated an overall fine motor slowing, with the motor component being more affected in the major depressive disorder patients than in the CFS patients, while cognitive impairments were similar.

We further examined psychomotor function in well-characterized female CFS patients without current major depression and control individuals by means of the earlier mentioned writing tablet-method, with a special focus on the inhibition of automatic responses (Van Den Eede et al. 2010). This factor was assessed by introducing "conflicting patterns" (i.e. patterns that were difficult to draw from the preferred left to right). As a result, CFS was significantly associated with longer reaction and movement times. However, there was no interaction between disease status and conflicting character of the patterns. Taken together, these performance data on the figure-copying tasks provided confirmatory evidence for psychomotor slowing in CFS, but not for a disturbed inhibition of automatic responses.

Neuro-endocrine dysfunction

There is evidence for a hypofunction of the hypothalamic-pituitary-adrenal axis in a proportion of the patients with CFS, despite the negative studies and methodological difficulties. Mild hypocortisolism, blunted adrenocorticotropin response to stressors and enhanced negative feedback sensitivity to glucocorticoids are the main findings (Van Den Eede et al. 2007).

Several underlying mechanisms have been proposed. In a study by Gaab et al., patients with CFS showed an enhanced and prolonged suppression of salivary free cortisol after the administration of a low-dose of dexamethasone (0.5 mg), pointing to enhanced sensitivity to the negative feedback of glucocorticoids at the pituitary level. In accordance with these findings, we observed lower salivary free cortisol responses in the combined low-dose dexamethasone/corticotropin-releasing factor test in CFS patients than in control individuals (Van Den Eede et al. 2008). However, this effect was only clearly present in CFS patients without a history of childhood trauma.

The further research of our research group will be focused on longitudinal characteristics of the neuro-endocrine dysfunctions in CFS, on the validity of functional tests and on the effects of several clinical factors, such as: major depression, fibromyalgia and childhood trauma.

Genetic vulnerability

There is evidence for a genetic vulnerability in CFS. In a family history study by (Walsh et al. 2001), first-degree relatives of CFS patients showed significantly higher rates of CFS compared with the relatives of control individuals. Furthermore, a twin study on chronic fatigue, (Buchwald et al. 2001) assessed the role of genetic and environmental factors in unexplained chronic fatigue. It was reported that the concordance rate for idiopathic chronic fatigue was 55% in monozygotic and 19% in dizygotic twins with chronic fatigue not explained by medical or psychiatric conditions (estimated heritability: 51%), pointing to a genetic vulnerability.

As the heritability is relatively low in CFS, association studies are more appropriate than linkage studies to identify disease-related genetic variations. Only a few studies have focused on candidate genes in the neuro-endocrine system. Positive associations have been reported for genetic variations in the corticosteroid binding globulin, the glucocorticoid receptor, the serotonin transporter gene and serotonin receptor subtype 2A (for review, see (Van Daele et al. 2010). However, confirmation of these findings in larger CFS-populations is necessary, as well as research on the functional implications of the related genetic variants.

Our research group collected DNA in a well-documented tertiary CFS-sample (n > 200), in collaboration with the CFS-reference centre of the Antwerp University Hospital and with the Department of Psychiatry of the Catholic University of Leuven. We will perform association studies in candidate genes in the neuro-endocrine system and in the immune system. In addition, we also will explore the interactions with clinical factors, such as: disease severity, major depression and childhood trauma.

Addiction

Substance use disorders and related (non-chemical) addictive disorders are highly prevalent in the general population and the related costs both for society as the individual patient and their family is enormous. In addition these disorders are highly comorbid with other psychiatric (and somatic) disorders. Thus research into the pathogenesis and treatment of addictive processes are within the core-business of psychiatric research. Within CAPRI, several research projects are focusing on different aspects of addiction.

Cognitive research line

There is growing evidence that impairments in cognitive functions play a major role in the development, course and relapse of substance abuse disorders (Dom et al. 2005; Dom et al. 2006a; Verdejo-Garcia et al. 2008). In particular, functions that involve control over one's own behaviour (impulsivity versus self-regulation), and over behaviour when confronted with motivationally relevant drug cues (craving) are related to relapse in recent studies. In addition, recent

findings suggest that these deficits within (neuro)cognitive function may underlie a vulnerability to develop both SUD and other (externalizing) psychiatric disorders (ADHD, cluster-B personality disorders) (Dom et al. 2006b). Based upon these recent findings a research line has been implemented within the CAPRI-institute focusing upon the role of these cognitive functions related to self-regulation.

In a first approach we are interested in the role of neurocognitive functionality as a risk factor with respect to relapse after treatment of substance abuse. Indeed, the identification of (individual) risk factors that could predict relapse liability is of utmost importance within the framework of substance abuse treatment. Up to now many clinical features, e.g. age at onset or addiction severity, have been explored in this respect. However, none of these clinical features has proved to be consistent predictors of relapse. Recently a limited number of studies have suggested the use of neurocognitive measures (Verdejo-Garcia et al. 2008). Based upon these findings we developed and implemented a longitudinal research project exploring the relation between patient's performances on cognitive tasks of decision making and impulse control and their risk on relapse after treatment. Within two distinct patient populations, respectively polysubstance (illicit drug) abusing inpatients and pathological gamblers in outpatient treatment, the relationship will be explored between baseline, neurocognitive measures and substance use (or gambling) outcome three months after treatment.

A second project explores the role of impulsivity and cognitive functioning in a randomized, double-blind, placebo-controlled trial of modafinil for alcohol dependence. Modafinil is a known cognitive enhancer and wake-promoting agent that has been used as an augmentation strategy in the treatment of a variety of psychiatric disorders such as depression and schizophrenia (Joos et al. in press). In this project, alcohol dependent patients are randomized to a single morning dose of modafinil (300mg/d), or matching placebo, for 10 weeks. Both neurocognitive tests (on impulsivity and overall cognitive functioning) and self-report questionnaires are administered before, during and after treatment. Patients are followed up 6 months after treatment, to measure relapse rate. Primary outcome variables are test performance, craving ratings and relapse. It is expected that modafinil improves cognitive functioning, increases time to first relapse and reduces relapse rates and relapse severity. This project is part of a larger, translational, research project in collaboration with the Amsterdam University. The same paradigm is used both within an animal and neuroimaging research design. The final goal of this large, translational project is to acquire more knowledge into the basic neurobiological pathogenetic processes that lead to alcohol addiction and its relation with possible new treatment approaches.

Psychiatric comorbidity

Substance use disorders are highly comorbid with other psychiatric disorders. Currently three projects focus on different aspects of co-morbidity.

CAPRI coordinates the Belgian participation in the International ADHD and Substance Abuse prevalence study (IASP). This large international study has its central coordination by the International Collaboration on ADHD and Substance Abuse (ICASA), Amsterdam. The study aims to document the prevalence of adult ADHD in different countries within populations of patients referred for addiction treatment, and to gather knowledge about the relationship between ADHD and the onset and course of substance use disorders, including identification of genes. In addition, the study examines the accuracy and validity of screening and diagnostic instruments for ADHD within substance abusing patients.

Polydrug abuse and dependence is an increasingly prevalent pattern of substance abuse and clinical reports suggest high levels of psychiatric comorbidity within these patients. We investigate the prevalence of mental health disorders within a population of treatment seeking polysubstance abusers. This study into "dual diagnosis", in close collaboration with the University of Ghent, will further elaborate on the findings of an earlier study within CAPRI that has been concluded recently and was supported by the Belgian Federal Science Policy. In this study the feasibility and outcome of integrated treatment programs for the treatment of dual diagnosis patients (schizophrenia and substance use disorders) has been evaluated (De Wilde et al. 2005).

Somatic comorbidity

In close collaboration with the department of gastroenterology and hepatology of the University Hospital in Antwerp (UZA) a project is running enabling objectivation of alcohol abstinence in the setting of liver transplantation for end-stage alcoholic liver disease. Alcohol consumption will be assessed by determination of ethylglucuronide (EtG), a stable metabolite of alcohol, in both head hair and pubic hair. The patients will be assessed at fixed time points both on the waiting list and after liver transplantation for a period of 2 years. It will assess the validity of known predictive models used in the psychiatric evaluation of patients for relapse of alcohol use (Dom et al. 2010). Furthermore, it will be determined whether detection of EtG in pubic hair is more sensitive in detection of alcohol intake, compared to head hair.

Forensic Psychiatry

In CAPRI, there are two spearheads of research in forensic psychiatry: first Routine Outcome Monitoring (ROM) in forensic patients, and secondly, the neurobiological examination of hormonal drug treatment in sex offenders. The ROM is an example of clinical research. It has a close relationship with daily

practice and caregivers, and could improve the scientific level of forensic psychiatric practice. The research on hormonal drug treatment in sex offenders is rather fundamental with tight neurobiological backgrounds. It will be set up in collaboration with the department of endocrinology.

ROM in forensic patients

The aims are (1) to emphasize the interaction between research and clinical practice; (2) to measure the efficacy of forensic psychiatric treatment regarding the risk of recidivism, the level of psychopathology, and quality of life; and (3) to introduce a dimensional approach to personality disorders. The following research questions are raised: What is the efficacy of the given treatment, in the context of psychiatric symptoms, quality of life, and risk of recidivism? Can we obtain a clearer view on the effectiveness of various treatment modules as part of the whole treatment, and how can we apply this effectiveness in practice?

Many research articles about the efficacy of forensic psychiatric treatment as a whole, have methodological pitfalls (e.g. (de Beurs & Barendregt 2008)). The aim of ROM is to collect data in a routine manner. The advantages of this method are that there is good evidence that interventions are efficient, that the data are easy to generalize, and that a clear distinction of patient groups that can benefit from a certain intervention, within the framework of treatment circumstances, can be made.

The main disadvantage is that ROM is a quasi-experimental design with less evident value concerning the effectiveness of treatment. According to de Beurs & Barendregt, we should combine three methods to investigate treatment processes: an infrastructure of ROM, with smaller Randomised Controlled Trials, and Single Case Designs. With regard to the implementation of the ROM, we suggest the use of Cyclic Effect Monitoring (CEM). This starts with a baseline measurement, based on risk assessment, behavioural observation, and other relevant instruments. Next, treatment goals are monitored and assessed periodically. And finally, feedback of the results will be given to the treatment team and will nourish the next cycle of the treatment process. An important remark here is that feeding back outcome only works well in so called 'flagged cases', this means in patients with poor treatment results. When this distinction is not made, poor results of feeding back outcome can be expected. An interesting structured review in forensic psychiatry was done by (Chambers et al. 2009). They investigated all trials and intervention studies published between 1990 and 2006. There was little evidence to support the measurement properties of commonly used instruments (in total 540 different instruments were used). It was surprising that the most common risk assessment instrument, the HCR-20, was hardly used as an instrument to measure outcome.

In this project the following hypotheses are made: 1) Forensic psychiatric treatment leads to lesser symptoms; (2) Forensic psychiatric treatment leads to the decrease of reoffending; (3) The decrease of psychotic symptoms leads to a reduction in aggression and risk of reoffending; (4) Lower scores on personality traits in patients with a (comorbid) personality disorder leads to a decreased risk of reoffending; (5) In comorbid psychotic offenders, no evidence can be found for a positive correlation between risk assessment and positive psychotic symptoms; and (6) The more symptoms there are, the lesser the Quality of Life is rated.

This research will be performed at the University Forensic Centre, Antwerp, and the Unité de Pyschopathologie Légale, Tournai (outpatient care facilities), and within a few years at the new forensic psychiatric hospitals of Ghent and Antwerp, and at the Centre Hospitalier Psychiatrique 'Les Marronniers' in Tournai. The CEM will last at least three years, with measurements each six or twelve months. In order to test the instruments to be used, a pilot study will be performed. We will use psychometric instruments within three domains: psychopathology, quality of life, and risk of reoffending.

Neurobiological examination of hormonal drug treatment in sex offenders

Quantitative outcome research of antiandrogenic drug treatment in sex offenders is rare and had methodological shortcomings. These hormonal drugs have dangerous side effects, so meticulous treatment is necessary. The research questions are: How effective is triptorelin in the reduction of sexual fantasies and the risk of reoffending? What can be said about the somatic and psychiatric consequences of triptorelin in the long-term in a Belgian sample of sex offenders treated with this drug?

In an overview of outcome studies, De Ruiter and Veen (De Ruiter & Veen 2006) questioned the limitations of these studies: inconsistent findings, severe methodological shortcomings, a doubt whether the participants were a representative sample of the total group of sex offenders; a lack of protocols in drug treatment (various drugs, various doses, and various treatment durations) (Van Hunsel & Cosyns 2002); the follow-up period was inadequate; and recidivism as a major outcome variable was operationalised in different ways (e.g. self-reports of sexual drive or activity, convictions or reportings. In conclusion, studies were almost incomparable, and were not cumulating concerning content (Van Hunsel & Cosyns 2002). Therefore, there is a strong need for protocols, which can be an algorithm or a decision tree, or guidelines.

This is an example of a longitudinal, prospective study using several measurements (CEM, or ROM). Besides the measurement of biological markers and an extensive anamnesis, instruments will be used with regard to personality traits and -disorders, sexual behaviour, sexual fantasies, and risk assessment.

CONCLUSION

CAPRI adds to the scientific evidence and clinical practice with original contributions in different fields: Child and Adolescent Psychiatry, Cognitive and Psychomotor Dysfunctions in Schizophrenia, fMRI in Schizophrenia, Cognitive and Psychomotor Dysfunctions in Major Depressive Disorder, Chronic Fatigue Syndrome, Addiction Medicine and Forensic Psychiatry.

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