1. Introduction

One of the great challenges in medicine — let alone psychiatry — is how to improve the outcome of schizophrenia. Over the last 50 years the use of dopamine receptor blocking drugs has made a very significant impact on the so called positive symptoms of the disease—hallucinations and delusions. However schizophrenia is also characterized by two other sets of problems, negative symptoms and cognitive impairment. These elements of schizophrenia are often a major source of disability and as yet there are no known treatments for them.

The ECNP each year hosts an open consultation meeting with experts in drug regulation, neuropsychopharmacology and clinical psychiatry to discuss issues of clinical importance. The meeting topic in 2012 was the cognitive dysfunction in schizophrenia and this report summarizes the output of the two day meeting.

2. Regulatory background

The revised European Medicine’s Agency (EMA) guideline on clinical investigation of medicinal products in the treatment of schizophrenia allows cognition to be targeted as a claim. Little specific directions are given, and no claims have yet been granted to any product. Therefore, strategies and trial design are largely open for discussion, with hardly any data to rely on as reference (CHMP, 2012).

The construct of cognition is diverse, ranging from attention, learning and memory to the ability to have social bonds and activities, and is used in many different ways. In the article by Millan et al. (2012b), an overview is given of its significance in the specific psychiatric domains, demonstrating that different drugs may target different aspects of the construct. This makes it difficult to define beforehand what should be the target with its inherent endpoint.

In regulatory guidelines, cognition as safety measure can be found in the guidelines for depression, insomnia (memory), panic disorder, bipolar disorder, and schizophrenia. No definition is given, but it is not surprising that some safety data on cognitive impairment or sedation are required for all psychotropic drugs.

For an efficacy claim, cognition is mentioned in the guideline for ADHD (inattention), Parkinson’s disease (executive function), epilepsy, Alzheimer’s disease (memory, learning), and schizophrenia (a.o. social cognition). Here, some differentiation is made, although used in an arbitrary way throughout the disorders.

It is more or less a regulatory rule, that, for a claim to be granted to a drug that treats a symptom domain within a disease entity, the relevance of the specific drug effect in terms of patient benefit, should be clear. In that respect, drug efficacy should not only be demonstrated as symptom improvement, but also expressed as improved functioning of the patient, e.g. the patient is more successful in school or work, stays independent or is being self-supportive etc. On one hand, this is to avoid polypharmacy and pseudospecificity, on the other hand this is becoming more of a regulatory/industry debate in those disease areas where surrogate endpoints would suffice over years, but outcome studies demonstrate the drugs to be counterproductive to some end. Therefore, regulatory authorities often take a cautious approach.

Cognitive function in schizophrenia is broadly impaired, and it will depend on the investigational drug whether the target will be at the level of e.g. working memory and executive functioning on one end of the spectrum, the more social cognition at the other end of the spectrum, or otherwise. From a regulatory perspective, the requirements are similar, there should be symptom- and functional-improvement demonstrated.

With little data to rely on in schizophrenia, ADHD and Alzheimer’s disease, may serve as examples of how these goals can be met. ADHD and AD are primarily cognitive disorders, albeit that the type of cognitive dysfunction is quite different as well as the type of studies requested for drug licencing. Several drugs are licenced for both disorders, where at least in Alzheimer’s disease both endpoints are met. The wide use of ADHD medication and attention to the safety profile of the drugs have issued the regulatory guideline in 2011 where the functional outcome measure is made a requirement.
Drugs in ADHD are usually effective in weeks, whereas drugs in AD are effective in months. For a functional outcome measure the time component is crucial. Attention may respond quite fast to cognitive enhancers, but whether this effect translates in better functioning remains to be seen over time. Therefore, in clinical trials the symptom improvement can be demonstrated in weeks, whereas the functional improvement should be demonstrated in longer term studies, usually in those used to demonstrate maintenance of effect. A dual endpoint is required, but not necessarily a co-primary endpoint. A primary and key-secondary endpoint may suffice, provided that in the end, both outcomes point in the same direction. If improvement of cognition takes some time, such as in Alzheimer’s disease, both endpoints can be met after 6 months, which is the standard length of a trial for symptomatic improvement in Alzheimer’s disease.

For schizophrenia, a trial duration of 6 months has been proposed in the guideline for a specific claim on cognition. This is considered sufficient to meet both endpoints, although the effect in cognition per se may be seen earlier. It is expected that drugs will be tested in the add-on design setting, i.e. add-on to conventional antipsychotic drugs, which offers the opportunity to use placebo control over a prolonged period of time for a fair estimate of both efficacy and safety.

For the primary endpoint, like in AD, a cognitive test battery is accepted, whether MATRICS or other. The effect, however, should be demonstrated on the whole battery and not solely on a subset of tests or single items. Although the primary endpoint is reasonably defined, the largest challenge is to define the functional outcome measure. It is not expected that functional outcome in schizophrenia should be in the range of for example the ability to start or keep a job, build a social network etc. Some experience may be taken from AD, where preservation of function is a valuable goal. In that respect, the treatment of a younger patient population, or a population with a relative recent onset of disease may be preferred.

By taking this approach, responders may be defined as patients with a certain improvement on cognition and function, where the latter could also be defined as at least no further deterioration.

Many open questions remain where ongoing research may provide some answers. The regulatory view is focussed on new drugs that, in affecting cognition, can demonstrate an added value to the patient benefit.

3. Approaches to cognitive enhancement in schizophrenia

Major advances have been made in understanding neuro-modulation of the prefrontal cortex in relation to the clinical and preclinical neuroscience of cognition (Robbins and Arnsten, 2009). However these have not so far translated effectively to the clinic in the context of cognitive enhancement of schizophrenia. For example, there is considerable evidence from the work of Goldman-Rakic and others that the dopamine D1 receptor is crucial to working memory and attentional function in monkeys and rodents, and for an optimal level of dopamine activity for this cognitive capacity which can be severely impaired in schizophrenia. The neural basis of this function is also well understood at the cellular and molecular levels. Moreover, this basic neuroscience research has translated quite well to demonstrations of working memory modulation by drugs such as methylphenidate and L-Dopa in human volunteers, and patients with Parkinson’s disease and attention deficit/hyperactivity disorder (ADHD).

One key demonstration is that methylphenidate may enhance the ‘efficiency’ of neocortical function by virtue of its actions in improving performance while reducing cerebral blood flow requirements in networks engaged by cognitive tasks. The discovery of polymorphisms that affect prefrontal dopamine function, such as catechol-o-methyltransferase, is also consistent with the ‘inverted-U’ shaped function linking baseline dopamine activity to cognitive function. Similar translational success has been shown for ‘fronto-executive’ functions such as inhibitory response control, as measured by tests such as the stop-signal reaction time paradigm. Performance on this task is improved by the selective noradrenaline reuptake inhibitor atomoxetine and by the atypical stimulant modafinil in both humans and rodents trained on analogous procedures.

Modafinil, which is used clinically in the treatment of narcolepsy, does in fact have some cognitive enhancing effects in non-sleep-deprived human volunteers, including planning on the CANTAB version of the ‘Tower of London’ test. This performance-enhancing effect is also mediated in part by adrenergic receptors. As modafinil appeared as equivalently effective in laboratory tests of cognition as atomoxetine and methylphenidate for patients with adult ADHD, it was also tested in studies on chronic and first episode schizophrenia by Sahakian and colleagues. Some significant effects in tests of cognition were also found in these groups, including an improvement in a test of cognitive flexibility related to the Wisconsin Card Sort Test called the intra-dimensional/extra-dimensional shift test. This test has now translated effectively across four species including humans, monkeys, rats and mice, thus potentially enabling comparative drug testing cross-species. Remarkably, this has enabled a ‘back-translation’ studying a model of schizophrenia (chronic PCP treatment) in which modafinil reversed the cognitive deficit (Goetghebeur and Dias, 2009). This example illustrates the potential of this area and provides a good model for the design of future studies of potential cognitive enhancement in schizophrenia.

4. Assessment strategies in clinical trials: update on designs and outcomes

There are many alternatives for cognition outcome measures in schizophrenia clinical trials. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is considered to be the gold-standard outcome by the United States FDA Psychiatry Division, and has also been supported by the EMA. There are other batteries that can be utilized; however FDA leaders have generally stated that these outcome measures would need to be justified.

The goals of the National Institute of Mental Health MATRICS Initiative were to (1) create a standardized cognitive battery to be used in clinical trials that represents a consensus among experts, (2) define optimal experimental
designs, (3) facilitate a path for FDA approval of cognitive enhancing compounds in schizophrenia, and (4) attract large pharmaceutical companies to focus efforts on this important unmet clinical need. Over the past few years, these goals have largely been realized. However, no cognitive enhancing compound for patients with schizophrenia has yet received regulatory approval.

One issue that arises with regard to the absence of an approved medication for cognitive deficits in schizophrenia is whether the current outcome measures are sufficient. The methods for evaluating cognitive endpoints in clinical trials have been reviewed previously. The general strategy for evaluating these endpoints are to consider six areas: (1) implementation of the test battery including missing data rate, tolerability for patients, and practicality for testers; (2) sensitivity to the relevant cognitive deficits in schizophrenia; (3) reliability; (4) magnitude of practice effects; (5) the relation of the test battery outcomes to co-primary measures of functional capacity; and (6) most importantly, sensitivity to treatment effects. Previous data (Keefe et al., 2011; Nuechterlein et al., 2008) have indicated that the MATRICS battery clearly meets the first five of these criteria.

There have been questions about the sensitivity of the MATRICS battery to treatment effects and whether other strategies may be more effective, particularly in early phase studies. It is important to keep in mind, however, that the tests chosen for the MCCB are well known to neuropsychologists and there is a vast literature demonstrating the sensitivity of these measures to both improvements and worsening based upon clinical state and medication effects. One strategy that has been forwarded but rarely utilized is to focus the cognitive endpoint on a small set of standard tests that is enhanced with cognitive neuroscience measures that assess the targeted cognitive mechanisms.

Data from large sample studies suggest that a sensitive composite score can be developed from a small number of tests (Keefe et al., 2006b). This strategy would then enable trial designs to have the time and resources to include additional tests that might be sensitive to very specific cognitive effects (Hilt, 2008).

A drawback of this strategy is that the relationship between improvement in very specific neurocognitive tasks and the desired functional outcomes is not determined. Further, this strategy is challenged by the common practice of pharmaceutical companies to design studies that include Phase 3 outcomes in their Phase 2 studies.

The relationship of social cognition and neurocognition and their use as endpoints in clinical trials has been a focus of recent research (Hoe et al., 2012; Fanning et al., 2012). While the recommended endpoint for the MATRICS battery has been a composite score derived from all seven domain scores, recent data suggests that social cognition may be best separated as a clinical endpoint. The MATRICS group is currently preparing a proposal to use a 6-doman “neurocognitive composite score” as an alternative endpoint that excludes social cognition. This approach has been developed due to data suggesting that social cognition with the MSCEIT Managing Emotions test may be difficult to assess outside of the United States (Rapisarda et al., in press), and that social cognition may respond differently to treatment than neurocognitive measures (Bowie et al., 2012).

The other issue to be addressed in this report is an update on the current cognition clinical trial designs for schizophrenia drug development. Most of the completed and ongoing clinical trials have focused on adjunctive “co-treatment” designs (Keefe et al., 2013). These designs were described in detail at the FDA-NIMH-MATRICS conference in 2004 (Buchanan et al., 2005) and have been updated (Buchanan et al., 2011). While many of the results from these designs have been negative, there are many ongoing studies (Keefe et al., 2013).

However, there have been recent findings reported in abstracts and conferences suggesting that nicotinic alpha-7 agonists may demonstrate efficacy (Hilt, 2011; Hosford et al., 2011). These interventions have demonstrated efficacy on cognitive measures including the CogState Computerized Test Battery and the MCCB, as well as on co-primary measures such as the Schizophrenia Cognition Rating Scale (SCoRS).

One important methodological consideration is that the efficacy of the SCoRS appears to be enhanced by the inclusion of informant ratings in the SCoRS outcome (Hilt, 2011). Another issue that has so far received very little attention from clinical trialists and researchers alike is the optimal study designs for the so-called “broad spectrum” compounds that target psychotic symptoms and cognition with a single medication.

The challenges of overcoming issues of pseudospecificity have largely been viewed as insurmountable, which is regrettable since a product that improves cognition and symptoms would be highly beneficial for patients with psychotic disorders. Multiple studies may be required, including one that treats patients with acute illness and one that treats stable patients switched to a new compound. However, a hybrid clinical trial design could be implemented. Such a design could examine a drug’s acute efficacy in patients with exacerbated illness over a short period of time such as 6 weeks by assessing symptoms and cognition at baseline and 6 week follow-up, and then examine long-term cognitive effects by using the 6-week follow up assessment as a baseline for long-term cognitive enhancement.

Some recent work suggests that there are compounds that may have beneficial effects for cognition and psychotic symptoms alike. BL-1020, a drug that combines peripherally acting GABAergic mechanisms, has been reported to improve symptoms in cognition (Geffen et al., 2012). In this trial, BL-1020 demonstrated efficacy over a 6-week time period with regard to symptoms and cognitive measures. In addition, there were medium sized correlations (r=0.34) between cognitive improvement and symptom improvement as measured by the PANSS, suggesting that a purely orthogonal effect on cognition and symptoms was not demonstrated. However, in a subgroup of patients treated for a longer time period, BL-1020 continued to improve cognition. These hybrid clinical trial designs may help to examine the efficacy of broad spectrum agents.

A lingering question that remains is the overlap between cognition and negative symptoms. The regulatory implications of a drug that concurrently improves cognition and negative symptoms have not been determined. A number of studies have demonstrated that a shared variance between cognitive impairment and negative symptoms is approximately 10% (Keefe et al., 2006b; Addington et al., 1991). The causal relationship between cognition and negative
symptoms is undermined and is likely to be bi-directional. Researchers and regulatory representatives continue to work on the issues that this topic stimulates (Marder et al., 2011; Laughren and Levin, 2011).

5. Clinically meaningful change and the crisis of co-primary outcomes

One of the great challenges in cognition clinical trials is the demonstration that any cognitive benefit has clinical meaning. The definition of a clinically meaningful change is not straightforward. For example, a recent symposium on “Defining Clinically Meaningful Effect for the Design and Interpretation of Randomized Clinical Trials” was held at the International Society for CNS Clinical Trials and Methodology 8th annual meeting, with a variety of perspectives on what a clinically meaningful change is (www.isctm.org). Statisticians at that meeting agreed that a well designed randomized clinical trial reporting a statistically significant difference between groups, even at a high level of statistical significance, should not be considered to be clinically significant (Kraemer and Kupfer, 2006). The question of clinical significance is open to a variety of interpretations, but largely depends upon the demonstration of a benefit that is visible to patients, family members, and health care providers.

Regulatory agencies addressing this issue in Alzheimer’s disease trials have generally required that a new compound demonstrate not only a cognitive improvement but also an improvement on clinician-based impressions of change. This issue has important implications for the design of clinical trials, as a requirement of clinical significance on two endpoints requires additional statistical power, dependent upon the correlation among those endpoints (Offen et al., 2007). With regard to schizophrenia cognition trials, regulatory agencies have adopted the position that concurrent change on a co-primary measure of functional capacity will be required for approval for a neurocognitive drug for schizophrenia (Buchanan et al., 2005).

One of the most important crises in cognition schizophrenia trials is the absence of well-developed and well-validated co-primary measures. While regulatory agencies have expressed flexibility regarding which co-primary measures can be chosen, none have stood out as excellent candidates. Work from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group and others have examined the psychometric characteristics of a variety of measures, including interview-based measures of cognition and laboratory-based measures of functional capacity, which is defined as a clinical demonstration that a patient has the capacity to demonstrate changes in functioning in the community. No regulators have expressed that a change in real-world function is necessary for registration given the fact that these types of changes are unlikely to occur during the course of even a 6-month clinical trial.

The criteria of evaluating the validity and value of co-primary measures includes (1) good test-retest reliability, (2) meaningful correlations with cognitive performance, (3) meaningful correlations with real-world functioning, (4) practicality for experimenters, (5) tolerability for patients, and (6) sensitivity to pharmacologic intervention (Buchanan et al., 2005; Green et al., 2008). A recent empirical comparison of a variety of potential co-primary measures, sponsored by the National Institute of Mental Health and executed by the MATRICS group compared six different measures. These were the Test of Adaptive Behavior in Schizophrenia (TABS), the UCSD Performance-based Skills Assessment (UPSA), the Independent Living Scales (ILS), and three interview-based measures, the Cognitive Assessment Interview (CAI), the Global Assessment of Function from CAI, and the CGI for Cognitive Impairment. The conclusions of this empirical study were that the UPSA had the best psychometric characteristics, with test-retest interclass correlations of 0.74 and a strong correlation with cognitive performance at $r=0.67$. Furthermore, the UPSA received high ratings for practicality and tolerability. However, the UPSA has some weaknesses. It was largely designed for elderly patients with schizophrenia, and a substantial minority of patients may do so well on the UPSA that medium to large benefits are unlikely during the course of the clinical trial. Further, the international version of the UPSA, called the UPSA-brief, only has two domains and may be further limited in its capacity to demonstrate improvement. This limitation has been demonstrated empirically (Keefe et al., 2011). However, the UPSA has the capacity to be sensitive to treatment-related improvement, as recently demonstrated by Javitt et al. (2012).

Interview-based assessments have also demonstrated promise. One of the drawbacks of these instruments is that their relationship to cognitive performance has been limited, especially if informants are not present to report on a patient’s level of cognitive function (Keefe et al., 2006a; Green et al., 2008). Two measures that have been used most frequently have been the Cognitive Assessment Interview (CAI) and the Schizophrenia Cognition Rating Scale (SCoRS). The benefit of the SCoRS is that it is a shorter instrument requiring only about 12-15 min of interview time with a patient and an informant; however the correlations with cognitive performance in the absence of an informant are weak. On the other hand, the CAI is a longer instrument and has stronger correlations with cognition if an informant is not available and the ratings rely on a patient interview only (Ventura, et al., in press). Recent work, however, has demonstrated that the SCoRS may be sensitive to cognitive benefit (Hilt, 2011). Interestingly, the efficacy of treatment was particularly strong ($d=0.51$) when an informant was able to provide SCoRS information.

While recent reports of the efficacy of these instruments demonstrate their potential promise, alternative methodology should be developed. Some examples are virtual reality assessments that measure a patient’s ability to navigate through a virtual functional world, such as a supermarket shopping trip (Fox et al., 2011), real-time assessments such as experience sampling or Ecological Momentary Assessments (Swendsen et al., 2011) or enhanced versions of current instruments that may increase variability and potential ceiling effects.

6. Cognition, abnormal development and schizophrenia

For the last few decades cognition has been on the cutting edge of research in mental health, as it has been considered one of the key points for the diagnosis and treatment of mental
disorders. Ever since Kraepelin (1919) first used the term “dementia praecox”, cognitive impairment has been described as a core feature of schizophrenia, which has an impact on relational and vocational spheres and social adjustment, and has been related to poorer prognostic factors (Heinrichs and Zakzanis, 1998; Reichenberg et al., 2005; Szoke et al., 2008). Thus it has been included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as one of the severity dimensions of symptoms in schizophrenia (American Psychiatric Association, 2012). This has been done assuming that the relative severity of cognitive impairment varies during the course of the illness and among patients, which will potentially be of great clinical value and also be of research utility.

But when trying to elucidate its implication for the course of the illness or even its relationship to some other developmental processes, cognition is still in the spotlight of current research, as some questions that still have to be clarified have arisen: Is this cognitive decline specific to schizophrenia? Which key cognitive features determine the course of the illness? What degree of severity determines diagnosis? And above all, is cognition the key to the link between abnormal development and schizophrenia? Or stated in another way, are children and adolescents with abnormal neurodevelopmental trajectories at higher risk for developing schizophrenia if they also have cognitive impairment? And if so does any specific cognitive domain predict schizophrenia versus other neurodevelopmental disorders (psychotic or otherwise?)

There are currently two approaches to trying to clarify the exact nature of the relationship between cognition and schizophrenia. On one hand, some studies have shown that shared risk factors, including neurocognition, reflect genetic liability to developing schizophrenia and related disorders in childhood and adulthood (David et al., 1997; Van Os et al., 1998; Erlenmeyer-Kimling and Rock, 2000; Cannon et al., 2002; Toulopoulou et al., 2010; Owens et al., 2011). A substantial proportion of the phenotypic correlation between schizophrenia and cognition is known to be caused by shared genetic effects. Patients with schizophrenia and their unaffected relatives are significantly impaired in cognitive performance compared with healthy controls (Toulopoulou et al., 2010). In the period from 4 to 7 years of age, premorbid cognitive dysfunction in children who later develop schizophrenia represents a relatively stable indicator of genetic vulnerability to schizophrenia (Cannon et al., 2000a; Horwood et al., 2008). Lower IQ scores precede the onset of formal diagnostic symptoms (Cannon et al., 2000a; Horwood et al., 2008), together with abnormal childhood motor development (Erlenmeyer-Kimling and Rock, 2000; Cannon et al., 2002; Blanchard et al., 2010). Regarding its relationship with other developmental risk factors, no association was found between lower IQ and obstetric complications (Cannon et al., 2000b). Furthermore intellectual asymmetry in IQ was found in first degree relatives — with a relative superiority of verbal skills to spatial skills — which could represent a putative endophenotype of schizophrenia (Kravariti et al., 2006). These cognitive impairments were also found in the offspring of patients with schizophrenia, specifically in the attention domain (Cornblatt et al., 1999), and their siblings — specifically in working memory — which supports their genetic liability (Goldberg et al., 2003).

On the other hand, the main aim of neuropsychological research in psychosis is to identify concrete patterns of cognitive deficits associated with specific psychotic diagnoses. In a cohort study that examined cognitive function at 18 years of age in 109,643 Swedish conscripts, the authors failed to find a linear association between most tests of intellectual functioning and the risk for schizophrenia, but they did find that the association was stronger for schizophrenia than for non-schizophrenic non-affective psychosis (Gunnell et al., 2002). Findings on specific cognitive profiles can point to cognition as a marker of the illness (Gourovitch et al., 1999). Neuropsychological deficits are present in schizophrenia and bipolar disorder (Zabala et al., 2010; Lewandowski et al., 2011; Bombin et al., 2013; Millan et al., 2012a). Even though comparative studies in an adult population (Krabbendam et al., 2005; Schretlen et al., 2007) showed that patients with schizophrenia and bipolar disorder have a qualitatively similar profile of cognitive deficits (functions preserved versus impaired), it also showed that patients with bipolar disorder performed quantitatively better in cognitive tasks than patients with schizophrenia. Differences between both diagnostic groups seem to persist even when controlling for clinical and demographic characteristics (Palmer et al., 1997; Heinrichs and Zakzanis, 1998; Rund, 1998; Cornblatt et al., 1999; Verdoux and Liraud, 2000; Martinez-Aran et al., 2002; Quraishi and Frangou, 2002; Addington et al., 2003; Balanza-Martinez et al., 2005; Goldstein et al., 2005; Hoff et al., 2005; Joyce et al., 2005; Osuji and Cullum, 2005; Torrent et al., 2007; Szoke et al., 2008; Zabala et al., 2010).

However, it is not clear if onset and progression differ between diagnostic groups. Preliminary findings suggest that neuropsychological functioning in patients with childhood or adolescent onset schizophrenia and bipolar disorder do not improve over time, thus showing similar cognitive profiles at the two-year follow-up after the first episode of early-onset psychosis (Bombin et al., 2013). Social cognitive dysfunctions have also been used to characterize cognitive profiles among psychiatric disorders, but the complexity of the constructs and the variety of definitions make it hard to develop adequate tasks useful for addressing the disorder specificity of these impairments (Millan et al., 2012a). In addition, the potential use of social cognition as an endophenotype must also be examined by studying individuals at high risk and their relatives.

7. Can we develop interventions for neurodevelopmental aspects of schizophrenia?

Longitudinal studies have shown how grey matter maturational process is in line with the abnormal developmental course suggested by cognitive data (Nieto and Castellanos, 2011). Moreover, lack of age-related improvement in cognitive abilities echo brain imaging findings suggesting abnormalities in the brain's maturational trajectory (Frangou, 2010). An adequate functioning of higher cognitive skills is a prerequisite for normal cognitive development and daily functioning. It seems
unlikely that patients with schizophrenia, especially those with early onset, will reach normal cognitive functioning in the absence of remedial interventions.

Obviously there is the need of pharmacological trials for cognitive developmental aspects, especially in patients with early onset. Many pharmacologic targets have been identified for cognitive enhancing agents including those new approaches that have been directed towards neuroprotection and the facilitation of neuroplasticity (Goff et al., 2011). On the other hand, different programs of cognitive remediation therapy (CRT) have demonstrated relevant benefits in most studies as demonstrated by different meta-analysis (McGurk et al., 2007, Wykes et al., 2011). In order to integrate neurodevelopmental and clinical research data, comprehensive models like neuroconstructivism (Westermann, 2007) can be informative. For instance, suggesting critical periods may be important not only pharmacological treatments but also for cognitive treatments or suggesting the principles that remedial learning needs to be based on.

Traditionally, the understanding of the mechanisms that are involved in neural circuit impairments and its relationships with cognitive impairment has been the main strategy to discover new pharmacological targets for schizophrenia. An interesting alternative has been proposed recently by Swerdlow (2011) who suggested that therapeutic approaches for schizophrenia should diverge from the prevailing models and focus instead on a more practical treatment strategy. The elements of this are (1) systematic rehabilitative psychotherapies designed to engage healthy neural systems to compensate for and replace dysfunctional higher circuit elements, used in concert with (2) medications that specifically target cognitive mechanisms engaged by these rehabilitative psychotherapies, and (3) antipsychotic medications that target nodal or convergent circuit points within the limbic-motor interface, to constrain the scope and severity of psychotic exacerbations and thereby facilitate engagement in cognitive rehabilitation. Thus, Swerdlow (2012) stressed the importance to combine CRT and pro-cognitive pharmacology.

This approach suggests that specific pro-cognitive drugs could be ineffective when administered without the demands of cognitive therapies and nonetheless they can still be effective when delivered together with CRT as a synergy facilitator. Swerdlow proposed the lack of efficacy of pro-cognitive drugs could be due to the fact that those trials have being done using drugs that were designed to surmount neuropathological changes in schizophrenia (e.g., d-cycloserine Gottlieb et al., 2011). An alternative strategy is suggested: utilizing medications that enhance spared neural functions in these patients. Unfortunately, evidence showing the existence of those ‘spared’ healthy circuitries is still scarce and for that reason some specific research is needed.

Such new approaches would require a revision of regulatory guidelines to make such trials feasible and economically possible.

8. Autistic Spectrum Disorders and cognition enhancers

Autism Spectrum Disorder (ASD) is another difficult challenge that requires the development of cognition enhancers that may also work in schizophrenia. The aetiology and pathology of ASD are still unknown but recent data suggests a shared genetic basis. ASD shows wide clinical diversity, and case identification is still solely based on symptomatology. Hence clinical trials typically include samples of biologically heterogeneous patients. Nevertheless, recent reports suggest that new opportunities are emerging. Risk gene variants have been identified, some linked to synaptic function and neural connectivity. Also, animals modelling these genetic traits mimic behavioural and neuroanatomical phenotypes associated with ASD; and it is possible that these behavioural ASD phenotypes could be rescued by targeted molecular treatment. Further, potential biomarkers to aid clinical stratification have emerged from recent neuroimaging, eye tracking, and electrophysiological studies (including adults). In addition, abnormalities have been observed in neurochemical/peptide pathways that may link to abnormalities in brain development and behaviour. There is, therefore, now an opportunity to make progress on the development of new therapies for ASD, including both children and adults.

For example, recently there is reported evidence for anatomical and functional abnormalities in frontal lobe, basal ganglia and the limbic system (Ecker et al., 2012). Also neuronal integrity using proton magnetic resonance spectroscopy (1H MRS), is reported abnormal in people with ASD abnormalities in prefrontal lobe and were related to repetitive behaviours and social communication deficits (Murphy et al., 2002). Pilot data suggesting that neuroimaging may soon become a useful diagnostic aid in young adults with ASD with abnormalities in 5HT and GABA-A receptors being reported (Murphy et al., 2006; Mendez et al., 2013) and altered brain myelination and function in ‘at risk infants’ (Deoni et al., 2011). A multi dimensional approach seems the most appropriate (Ecker et al., 2010).

This preliminary work, is now being brought together with that of academic and industrial partners across the European Union in the basic and clinical sciences to develop a new platform for drug discovery (European Autism Interventions—A Multicentre Study for Developing New Medications; EU-AIMS) as part of the EU Innovative Medicines Initiative.

9. Pharmacological cognitive enhancement: wider implications

The drive to alleviate human cognitive deficits has given rise to multiple interventions. One of these is pharmacological cognitive enhancers (PCE), or drugs that are aimed at improving cognition and everyday performance in individuals who suffer from impaired cognition due to brain injury or neuropsychiatric disorders (Morein-Zamir and Sahakian, 2011; Sahakian et al., 2010; Sahakian, 2011; Insel et al., 2012).

These cognitive enhancing drugs are able to improve forms of cognition, such as working memory, not only in people with neuropsychiatric disorders but also in healthy people. This raises important societal neuroethical issues due to increasing lifestyle use of cognitive enhancing drugs by healthy people. (Sahakian and Morein-Zamir, 2007; Morein-Zamir and Sahakian, 2011; Greely et al., 2008; Hyman, 2011; Swanson et al., 2011).
Therefore, it is important to consider the potential harms of these drugs, for example substance abuse, unknown effects on the developing brain or coercion at school or work.

Nevertheless, with the rapidly developing field of pharmacogenomics we may be able to gain maximum benefits with minimum harms to the individual and society as a whole. Certainly, the benefits of safe and effective cognitive enhancing drugs to society, including the ageing population and people with neuropsychiatric disorders and brain injury, are great. As members of society we need to consider how these drugs may change our society and whether that change will be of benefit to all (Sahakian and Morein-Zamir, 2009; Morein-Zamir and Sahakian, 2009).

We conclude that the use of PCE will likely continue both within patient and healthy individuals in the foreseeable future. Information regarding actual use, benefits and harms in various populations is severely lacking. Therefore, more emphasis should be placed on obtaining the relevant empirical data, for example, by long term monitoring of effectiveness and side effects, and by accurate large scale surveys to assess actual usage. Mechanisms to obtain this information should be put in place. We propose careful consideration is essential of the short and long term benefits and risks for each group and each drug, and that overgeneralization due to insufficient information should be avoided. Likewise, some mechanisms should be in place for informing healthcare providers and potential users of the trade-offs and of the present lack of long-term conclusive information. In addition, education for users in regard to the risks of purchasing prescription only drugs via the internet needs to be provided. Finally, other forms of enhancing cognition such as education and physical exercise should be promoted (Beddington et al., 2008).

10. Conclusions

The treatment of the cognition deficits in schizophrenia is still one of major importance for which there are no proven therapies at present. The recent ECNP consensus has explored this issue with a view to identifying possible ways to improve the current rather dire situation.

Schizophrenia is a complex entity involving the interaction of genetic, environmental and epigenetic factors. At this research stage, the key link between cognition and other factors for diagnosis has yet to be found. Cognitive impairment is known to be present at the onset of the psychotic symptoms and to a lesser extent it has been also observed in individuals at high risk and their healthy relatives. Premorbid intellectual functioning seems to be the more predictive of cognitive ability related to the diagnosis of schizophrenia. There is no evidence of uniform cognitive decline during the early phase of the illness, and there does not seem to be specific cognitive impairment in different psychotic disorders. No qualitative differences are observed between cognitive performance in patients with schizophrenia, bipolar disorder and other psychotic disorders, but quantitative differences are observed in the extent of their cognitive deficits.

Much more research is needed using defined cognitive paradigms based on observable performance in activities of daily living and its relationship to other specific biomarkers that can help to elucidate the exact nature of cognition and its concrete role in the development of the neurodevelopmental disorders of schizophrenia.

From a regulatory perspective there is clear commitment to the concept and some recommended ways to establish efficacy. From a neuroscience perspective the situation is less clear although a symptom-led approach may be the most tractable: however the regulatory aspects of this need further clarification as conventional trial designs and outcomes may not be ideal for such innovation.

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