

CHAPTER 20

ATTENTION DEFICIT HYPERACTIVITY DISORDER: DEFINING A SPECTRUM DISORDER AND CONSIDERING NEUROETHICAL IMPLICATIONS

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INTRODUCTION

ATTENTION deficit hyperactivity disorder (ADHD) is thought to affect about 5% of children around the world, although many differences in diagnostic methods make its recognition and treatment highly variable across countries and regions (see Polanczyk *et al.* 2007). Prospective follow-up studies have shown that even though some children outgrow the disorder, a childhood diagnosis of ADHD is clearly a risk factor for a broad range of adverse outcomes, with extremes including drug abuse and juvenile delinquency (see Molina *et al.* 2008). For administrative reasons, more acceptable methods are needed for defining ADHD consistently, and for clinical reasons more precise definitions of ADHD are needed that predict adverse outcomes and can be used to focus treatments.

Traditionally, ADHD has not been conceptualized as a spectrum disorder, either by the diagnostic system developed and currently recommended by the American Psychiatric Association (APA 1994) or by the World Health Organization (WHO 1993). However, clinical heterogeneity of the manifestation of ADHD does fit into the spectrum approach used for other psychiatric disorders (see Maser and Patterson 2002; Cassano *et al.* 2004). Here we will consider the use of several spectrum concepts and some neuroethical issues that accompany each one.

What are the defining features of a spectrum disorder?

The criteria in the Diagnostic and Statistical Manual (DSM) and the International Classification of Disease (ICD) manual provide lists of criterion symptoms with a threshold set for the number of symptoms required for categorical diagnoses of disorders. The current version of DSM-IV (APA 1994) provides a few examples of spectrum disorders (e.g. related to variants of schizophrenia and depression), and dimensional adjuncts have been proposed for almost all disorders in revisions for DSM-V (see Helzer *et al.* 2008) that may be used to define more disorder-related spectra in the future. A prototype spectrum approach is presented by Maser and Patterson (2002) for depression. It provides for recognition of subthreshold cases when the presence of criterion symptoms is elevated but below the established cut-offs. They point out that in psychiatric diagnosis the fundamental difference between the categorical diagnosis and the dimensional approach is that a dimension of behavior "... associated with an illness, disease or disorder has no absolute, qualitative break between 'normal' and 'abnormal.'" They also point out that a continuum approach differs from both categorical and dimensional approaches by defining "...a statistical middle range as normal and departure away from 'normality'" (Maser and Patterson 2002, p. 868). Here we will consider how these different approaches can be used to define an ADHD spectrum based on the concepts of *categorical diagnosis* (see Maser and Patterson 2002), *dimension of symptom severity* (see Helzer *et al.* 2008), and *continuum of behavior* (see Swanson *et al.* 2009).

How are definitions of an ADHD spectrum related to neuroethics?

The Society for Neuroscience (2008) suggests that the topic of neuroethics differs from general biomedical ethics because it deals with "... brain-specific issues that touch no other area of science," including "new neuroscience technologies such as brain scanning" and "pharmaceuticals to manipulate cognition" (p. 62). This has clear relevance to the definitions of ADHD as a spectrum disorder. All three spectrum approaches are based on different underlying assumptions of neural bases of this disorder, and the neural basis for its most common treatment (with stimulant medication) is based on hypotheses about the effects of this class of drug on neurotransmitters and synaptic events as well as on neural networks of the brain. In our introduction, we will provide a brief review of some brain imaging and pharmacological treatment studies of ADHD to set the stage of consideration of brain-specific issues related to neuroethics.

What is the current consensus about cognitive and neural deficits in ADHD?

Hypotheses about specific brain processes that might underlie the symptoms of ADHD date back to era when the syndrome was labeled "minimal brain dysfunction" (Wender 1971).

In the 1970s (see Douglas 1972) and 1980s (see Sergeant and Scholten 1985), neuropsychological studies emphasized the cognitive components over the motor components. This was reflected in the modern diagnostic criteria in DSM-III (APA 1980) and the label used then, attention deficit disorder (ADD), which elevated the cognitive symptoms to be the essential features of the disorder over the motor symptoms that were used to define a subtype (ADD with Hyperactivity). In the 1990s, theories emerged that propose ADHD symptoms are manifested as a consequence of a core deficit in executive functions (Pennington and Ozonoff 1996; Barkley 1997). However, subsequently extensive neuropsychological research has shown heterogeneity of cognitive deficits within typical groups of children with ADHD (see Doyle *et al.* 2000). Additional scholarly reviews concluded that the preponderance of evidence did not support any "core deficit" theory but instead favors theories based on multiple cognitive deficits (e.g. Nigg 2005; Willcutt *et al.* 2005). In comparison to groups of children without ADHD or with other disorders, some ADHD individuals do not manifest any deficit on specific neuropsychological tests of executive function or even on a composite of a battery of tests, suggesting that executive function deficits are not necessary or unique components of ADHD.

Recent studies with neuropsychological batteries (e.g. Rhodes 2005; Rubia 2007) provide evidence of multicomponent rather than unitary deficits in children with ADHD. From the perspective of cognitive neuroscience, this heterogeneity of cognitive deficits is not unexpected, since prominent theories have proposed that the neural processes underlying the cognitive symptom domains of ADHD (impulsivity and inattention) are not unitary constructs. Tests have been developed to fractionate both impulsivity and inattention into component parts. For example, Winstanley and colleagues (2006) describe two general domains of impulsivity—impulsive choice and impulsive action—and Posner and Rothbart (2007) describe three general domains of attention—alerting, orienting, and executive control.

In the 1990s, brain imaging and molecular genetic studies of ADHD identified some abnormalities that supported modern neuroscience theories of the biological basis of the ADHD disorder as a dysfunction in neural networks of the brain and functions they serve, rather than specific brain regions or cognitive processes. The early studies provided evidence of deficits in a cortical–striatal–thalamic network modulated by the neurotransmitter dopamine (Castellanos 1997). In the National Institutes of Health (NIH) Consensus Conference on ADHD (NIH 1998), Swanson and Castellanos (1999) summarized the emerging evidence of presence of abnormal brain anatomy (reduced areas of key striatal, frontal, and callosal brain regions) and association with alleles of candidate genes, the dopamine transporter (DAT) and the dopamine receptor D4 (DRD4) genes. Over the ensuing decade, others have presented reviews to update these findings, which in general have been replicated and remained consistent with these early neural network theories of ADHD (see Castellanos and Tannock 2002; Bush 2010). There have been some advances to refine these theories of ADHD, which we have reviewed and discussed in detail elsewhere (Swanson *et al.* 2008a,b; submitted), so only a selected few will be discussed here.

Studies using functional magnetic resonance imaging (fMRI) revealed that in ADHD children (compared to controls) some brain regions involved in the performance of cognitive tasks were underactivated (e.g. frontal) lobes) and others overactivated (e.g. parietal), suggesting that ADHD children may compensate for cognitive deficits underlying the symptoms of inattention and impulsivity by using alternative neural processes to achieve some degree of attention and reflection (Durstun *et al.* 2003; Schulz *et al.* 2004; Schweitzer *et al.* 2003).

Recent studies (see Volkow and Swanson 2008; Volkow *et al.* 2009) of adults with ADHD using positron emission tomography (PET) and radioligands targeting the synaptic mechanisms of dopamine transmission have uncovered abnormalities in brain networks associated with processes of motivation (with involvement of dopamine transmission in the nucleus accumbens) as well as with processes of attention (with involvement of dopamine transmission in the caudate nucleus), suggesting a motivation deficit as well as an attention deficit may characterize individuals with ADHD.

Studies using reaction time (RT) tasks of cognitive control (e.g. the go/no-go task), response inhibition (e.g. the stop signal task), and conflict (e.g. the attention network task or ANT) have identified interindividual variance in task performance as one of the most prominent aspects of cognitive deficits related to ADHD (see Swanson *et al.* submitted for a review). The increased variance produced skewed distributions of RTs (see Leth-Steensen *et al.* 2000). These observations led to the speculation that long response times may be the result of lapses in attention that are cyclical with relative slow waves occurring every 20–40 seconds rather than the results of random events (see Castellanos 2005). Several studies have used Fourier analyses of RTs and have shown that the power in these low frequency bands is greater in ADHD individuals than in controls (e.g. see Di Martino *et al.* 2008). The slow oscillations in RTs may be related to brain networks (see Fox *et al.* 2006) that are considered to be task-positive (a dorsal network) and a task-negative (a ventral network). The dorsal network is activated during goal-directed task performance, and it includes the dorsal lateral and ventral prefrontal brain regions that are activated by a variety of cognitive tasks. The ventral network, described as a “default network” that includes the medial prefrontal, posterior cingulate, and lateral parietal regions, is deactivated when performing a task. At rest, the ventral default network is activated (“resting state”) and the dorsal network is deactivated, and during task performance the dorsal network is activated and the ventral network is deactivated. Sonuga-Barke and Castellanos (2007) proposed the default-mode interference hypothesis of ADHD: the ventral network may be deactivated when a RT task is initiated, but gradual recovery may eventually intrude on the activity of the dorsal network, and when a threshold is crossed a lapse of attention occurs and results in a long RT.

Effects of stimulant medication

The literature on the use of stimulant medications—amphetamine (AMP) and methylphenidate (MPH)—for the treatment of hyperkinetic disorder (HKD) and ADHD is enormous. In the 1990s, the number of articles was in the thousands and there were already more than 300 reviews. Swanson *et al.* (1993) used a “review of reviews” to synthesize the literature and summarized what should be expected (temporary reduction of symptoms of ADHD and management of some associated features—social, academic, and deportment deficits) and what should not be expected (large effects on higher order processes, paradoxical responses, prediction of response, absence of side effects, or improvement in the long-term). The “review of reviews” approach was also used by Conners (2002), who added contemporary reviews from through the early 2000s and summarized the consistency across time and methods about the effects on behavior (effect size approximately 0.74) and academic performance (effect size approximately 0.46).

From 1937, when the first use of stimulants was reported (Bradley 1937) until 2000 when the first use of modern controlled-release (CR) formulations was reported (see Swanson *et al.* 2000), the state-of-the-art practice of stimulant pharmacotherapy was based on multiple daily doses of immediate-release (IR) MPH. Three-times-a-day (TID) administration of IR-MPH for 7 days per week was used in the medication algorithm of the Multimodal Treatment study of ADHD (MTA). After titration based on the full range of doses from 5–20mg TID (see Greenhill *et al.* 1996), about 90% of all of the cases (children with diagnoses of ADHD Combined Type) showed a clinically significant short-term response, as expected from the massive literature (see Swanson *et al.* 1993; Conners *et al.* 2002) on response to stimulant medication. The relative benefit of medication management (MedMgt) over the non-pharmacological treatment, behavior modification (Beh), was maintained for the duration (14 months) of the treatment-by-protocol phase of the randomized clinical trial (MTA Group 1999). However, the relative benefit dissipated during the naturalistic follow-up phase of the MTA, and by the 3-year assessment there was no documented relative benefit of the initial assigned treatment (MedMgt vs. Beh) or of the actual or current treatment with stimulant medication (Jensen *et al.* 2007; Swanson *et al.* 2007a,b).

Brain imaging studies have suggested one of the primary sites of action of stimulant medication: a typical oral clinical dose of MPH blocks about 50% of the available DAT (Volkow *et al.* 1995, 1998), and significant increases in extracellular DA occur at clinically relevant oral doses of MPH (Volkow *et al.* 1999b, 2009a) and AMP (villemagne *et al.* 1999). This biochemical effect has profound effects on brain function, as shown by Volkow *et al.* (2008a) using PET and FDG (fluodeoxyglucose) to measure brain glucose metabolism in non-ADHD adults when performing a cognitive task: compared to placebo, MPH significantly reduced the task-related increase in glucose by 50%, suggesting increased focal activity that may enhance or impair performance on a task.

On some measures of response there may be cognitive enhancing effects of stimulants on non-ADHD (control of normal) individuals. Challenges to the hypothesis of a paradoxical response in children with ADHD have a long history. For example, Sahakian and Robbins (1977) developed the hypothesis that the clinical improvements in activity and attention were related to the normal action of the stimulants in producing stereotyped behavior. They also pointed out that stereotyped behavior increases with dose, and they suggested that as in animal studies this drug-response might merely reflect an increased rate of responding within a reduced number of response categories. In some cases this may be related to dose-related physical side effects that occur (e.g. tics, picking and biting, etc.) and cognitive side effects (overfocusing, anxiety, etc.), as well as loss of flexibility in cognitive tasks that is essential for good performance on some neuropsychological tasks that require reversals in cognitive strategies.

The hypothesis of a paradoxical response to stimulants was tested by Rapoport *et al.* (1978), who evaluated dose-related effects of d-amphetamine on ADHD and normal children and adults. They showed that the direction of response (e.g. decreased activity level) was the same in individuals with and without diagnoses of the clinical syndrome of hyperactivity that is now labeled ADHD. Robbins and Sahakian (1979) considered factors related to response to stimulants (dose, rate dependency, and stereotypy). They point out that effects of dose are likely to be manifested as a U-shaped curve, with low doses producing enhancement but high doses impairment. The Yerkes–Dodson law describes this relationship for tasks that are complex but not for simple tasks, which has been discussed in great detail recently by Diamond *et al.* (2007). Robbins and Sahakian (1979) also point out that rate

dependency may occur, which is stated as an inverse mathematical relationship between the frequency of a behavior and the relative effects of stimulants. They reported rate-dependent analyses for many studies in the literature, and discussed several complications in the analyses of data (e.g. use of baseline vs. placebo on the abscissa, the regression to the mean effect, etc.), and showed that the manifestation of rate dependent effects in these datasets was not invariant across the methods used to estimate its presence.

The general notion of cognitive enhancement has been questioned repeatedly and regularly over the past 50 years (see the reviews presented in the scholarly books by Grinspoon and Hedblom 1975 and Rasmussen 2008). Stimulants appear to produce a sense of well-being in many individuals (see Rasmussen 2008 for a description of Gordon Alles' response to the first ever dose of the newly synthesized drug amphetamine in 1929). Similar responses have been observed in modern studies of the drug methylphenidate (e.g. Bray *et al.* 2004 described the perception of well-being and benefit even in the absence of cognitive enhancement). Stimulants also appear to produce benefits on some tasks and in some individuals (see Mehta *et al.* 2004, who found that the enhancement was greatest in those who performed poorly on the laboratory tasks used for evaluation). However, literature on the effects of stimulants on individuals without ADHD is very sparse, and this leaves considerable uncertainty about the general effects of the non-medical use of stimulants.

The debate about cognitive enhancement and non-medical use of stimulant medication was revived recently by Sahakian and Morein-Zamir (2007), who proposed that "...scientists, doctors, and policy-makers should provide easy access to information about the advantages and dangers of using cognitive-enhancing drugs and set out clear guidelines for their future use" (p. 1157). This challenge generated discussion of important neuroethical issues in the scientific literature (see Greely *et al.* 2008; Swanson and Volkow 2008; Volkow and Swanson 2008) and in the popular press (see Stix 2009) about the non-medical use of stimulant drugs and the regulatory restrictions and laws that apply. These same issues about U-shaped dose-response curves addressed by Sahakian and Robbins (1977) and Robbins and Sahakian (1979) are still critical to consider in the current debate about the non-medical use of stimulants. In individuals with ADHD, the medical use may produce a U-shaped curve that would be the basis for titration to find the optimum dose, while in individuals without ADHD the non-medical use may produce a monotonic dose-response function (dose-related impairment) or a small enhancement followed by dose-related impairment. Here we will discuss how the consideration of ADHD as a spectrum can contribute to this debate.

DEFINING A SPECTRUM FOR ADHD: THREE APPROACHES

Categorical diagnosis in DSM-IV and ICD-10

The same set of 18 symptoms (see Table 20.1a) is used to make categorical diagnoses of ADHD by the DSM-IV criteria or HKD by the ICD-10 criteria. In both diagnostic systems, the gold standard is the clinical interview by which a fundamental categorical judgment is

made about each symptom—present or absent—dependent on whether its manifestation is severe enough to contribute to functional impairment. Another categorical decision is required by both diagnostic systems based on symptom counts and cut-offs set for the DSM-IV diagnosis of ADHD and for the ICD-10 diagnosis of HKD.

Despite the same symptoms, differences in decision rules make HKD a subset of ADHD. The decision rules have been described by Santosh *et al.* (2005), who provided details about how these decision rules address pervasiveness across settings and symptom domains, as well as impairment and comorbidity:

- 1) *Settings* For both DSM-IV and ICD-10 approaches, pervasiveness of symptom presence is required across settings, which for children are typically parent and teacher reports of behavior at home and school. For DSM-IV, the “Or” decision rule is used to define symptom presence (see Lahey *et al.* 1994): some symptoms must be manifested in more than one setting, but any particular symptom is counted if manifested in only one setting (e.g. at home or school). In contrast, for ICD-10 the “And” decision rule is applied (see Taylor *et al.* 1998): a symptom is counted only when manifested in more than one setting (e.g. at home and school).
- 2) *Symptom domain* In both DSM-IV and ICD-10 the same three domains (Inattention, Hyperactivity, and Impulsivity) are used to organize the 18 symptoms. The same nine symptoms are listed in the Inattention domain, but in DSM-IV the symptoms of impulsivity are merged with the Hyperactivity symptoms while in ICD-10 these two domains remain separated. Cut-offs are set for the two DSM-IV domains (at least six of the nine symptoms of Inattention and at least six of the nine symptoms of Hyperactivity/Impulsivity) and partial syndromes are defined (ADHD Primarily Inattentive or Primarily Hyperactive/Impulsive Type) as well as the complete syndrome (ADHD Combined Type). For ICD-10, the cut-offs are set for the three domains (six or more Inattention, three or more Hyperactivity, and one or more Impulsivity symptoms) and only a single syndrome (HKD) is specified.
- 3) *Impairment* DSM-IV requires some impairment in at least two settings, but ICD-10 has an additional requirement of overall impairment.
- 4) *Comorbidity* In DSM-IV the diagnosis of ADHD plus comorbid disorders is encouraged, but in ICD-10 the aim is to make a single primary diagnosis of HKD. For example, in DSM-IV diagnoses of comorbid internalizing disorders (anxiety and depression) are allowed if their criteria are met, but in ICD-10 the diagnosis of HKD is not recommended in the presence of internalizing disorders.

The DSM-IV decision rules already define an ADHD spectrum with provisions for a wide variation in the presence of the 18 criterion symptoms. At first glance (see Figure 20.1a), it may appear that the minimum symptom-count cut-off threshold for ADHD Combined Type (six from each of the two domains for a total of 12) is greater than for HKD (a total of ten from the three domains). However, this relationship may be reversed by the decision rule requiring pervasiveness across the two settings (home and school). This logically results in 36 setting-specific symptoms (see Table 20.1b and Figure 20.1b). We propose this dimension as an ADHD-equivalent of the dimension of symptom presence proposed by Maser and Patterson (2002) for defining subthreshold conditions in the spectrum of depression.

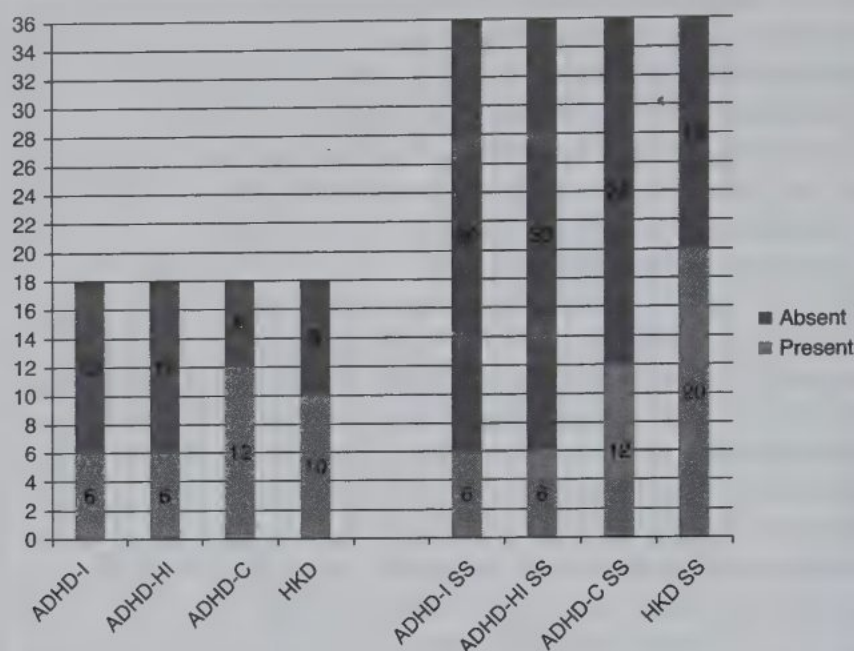


FIG. 20.1 Minimum thresholds for ADHD and HKD (a) Categorical diagnoses based on symptoms and (b) the ADHD spectrum based on setting-specific (SS) symptoms.

According to the application of the decision rules outlined earlier, the setting-specific symptoms required for a diagnosis of ADHD-Combined Type still would be six from each domain, but for the minimum this could be different items for the home and school setting for a total of 12, while for a diagnosis of HKD it still would be ten, but for the minimum this would be the same ten symptoms in both the home and school settings for a total of 20 (see Figure 20.1b).

What are the implications of the categorical (symptom count) approach in clinical application? Santosh *et al.* (2005) used the ICD-10 criteria and decision rules to evaluate the clinical sample of 579 children in the MTA (i.e. children with the categorical diagnosis of ADHD Combined Type based on a variant of the "Or" decision rule). The re-evaluation with the more stringent ICD-10 criteria resulted in diagnosis of HKD in only 25% of the MTA participants. Also, in a study of a population sample of 2452 German children, Dopfner *et al.* (2008) used DSM-IV criteria that identified about 5% of a population sample. They reported that only 25% of that group also met the ICD-10 criteria for HKD. The common finding of these two studies (i.e. a fivefold difference in the estimated prevalence) is consistent with the relative placement of ADHD and HKD on the proposed spectrum of 36 setting-specific symptoms (see Figure 20.1).

Some epidemiologic studies specifically have evaluated subthreshold manifestations of ADHD, defined operationally by the presence of three to five symptoms in one symptom domain (for subthreshold ADHD Inattentive or Hyperactive/Impulsive subtypes) or in both (for subthreshold ADHD Combined Type). In a recent example, Kim *et al.* (2009) evaluated ADHD in a random selection of ten schools in Seoul, Korea. Using the DSM-IV criteria and

Table 20.1 Eighteen symptoms and 36 setting-specific symptoms for the ADHD spectrum

Domain symptoms	a. Symptoms for categorical diagnosis	b. Setting-specific for spectrum evaluation
Inattention	1. Fails to attend to details	1. P1 2. T1
	2. Difficult sustaining attention	3. P2 4. T2
	3. Does not seem to listen	5. P3 6. T3
	4. Fails to finish	7. P4 8. T4
	5. Difficulty organizing tasks	9. P5 10. T5
	6. Avoids sustained effort	11. P6 12. T6
	7. Loses things	13. P7 14. T7
	8. Distracted by extraneous	15. P8 16. T8
	9. Forgetful	17. P9 18. T9
Hyperactivity	10. Fidgets	19. P10 20. T10
	11. Leaves seat in class	21. P11 22. T11
	12. Runs about or climbs	23. P12 24. T12
	13. Difficulty playing quietly	25. P13 26. T13
	14. Motor excess	27. P14 28. T14
Impulsivity	15. Talks excessively	29. P15 30. T15
	16. Blurts out answers	31. P16 32. T16
	17. Difficulty waiting turn	33. P17 34. T17
	18. Interrupts or intrudes	35. P18 36. T18

the DISC-IV interview, they found that the prevalence of the full categorical diagnosis of ADHD decreased with age, from about 7% in grades 1–3 to about 2% in grades 7–9, for an average of about 5% in school-aged children, while prevalence of subthreshold ADHD remained constant at about 9%. Thus, they also observed a substantial difference in prevalence of HKD and ADHD (see Figure 20.2), as has been observed in other countries, including Germany (Dopfner *et al.* 2008) and in the USA (Wigal *et al.* submitted).

What are some of the neuroethical implications related to such a large cross-national difference in prevalence of a condition considered to have a biological basis? Here we will discuss two neuroethical issues: first, at the population level, policy contributes to the large difference in “*administrative prevalence*” (the recognition and treatment rate) and second, at the individual level, clinical assessment contributes to *stigma and access to services*.

At the policy level, the decision rules for categorical diagnosis in DSM-IV and ICD-10 are determined by a top-down process based on clinical expertise rather than a bottom-up empirical process (see Helzer *et al.* 2008). The large cross-national difference in diagnosis may reflect differences in culture and custom that set policy rather than population differences in manifestation of the symptoms that have similar neural bases. The rate of diagnosis directly impacts rates of medication usage; in the US, where recognition and treatment rates are the highest, prescription stimulant medications (MPH and AMP) for ADHD represented two of the top five prescribed pediatric medications in terms of total expenditures (Stagnitti 2007), at a cost of more than \$1 billion in 2004. When resources for healthcare are limited, the relative needs and benefits of medications across conditions must be considered (National Institute for Health and Clinical Excellence 2008). Policy decisions—such as those made for the DSM-IV and ICD-10 decision rules—have neuroethical implications since they operate to affect the allocation of scarce resources.

Sartorius (2007) discusses how stigma (“the negative attitude based on prejudice and misinformation”) may be triggered by a marker of an illness, and he outlined ways to reduce stigma by reducing the visibility of markers and by increasing local and national efforts for

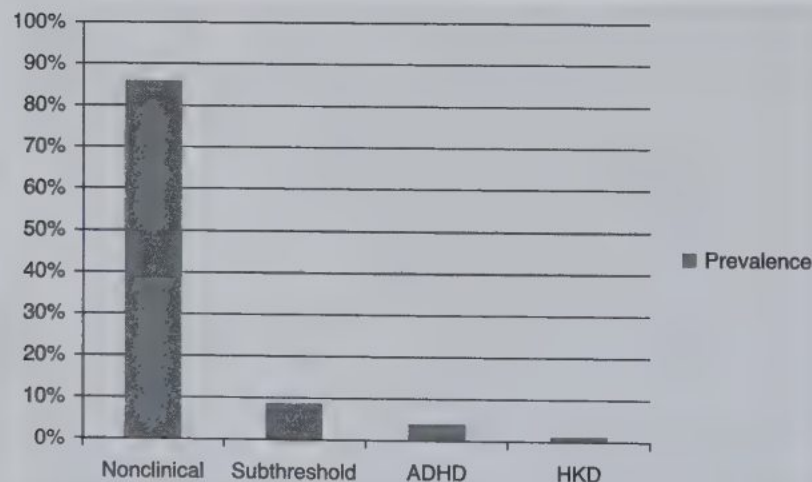


FIG. 20.2 Estimated prevalence of ADHD and HKD.

education and reduction of discrimination. In the ADHD area, over the past decade there are two good examples of successful efforts to reduce stigma. The first example is related to educational law. In the 1990s, a national effort in the US led to recognition of ADHD as a disability by Public Law 94-142, the Individuals with Disabilities Education Act (IDEA). Before the IDEA, ADHD was considered solely a medical condition and thus was not addressed in educational law, so a diagnosis did not qualify an individual for special services in the school setting where symptoms are manifested and may predominate. Some background on the prior educational law, the Education of the Handicapped Act (EHA), and details of the IDEA are summarized by Swanson (1992). ADHD was not considered a handicapping condition in the EHA, but when it was revised to become the IDEA, ADHD was considered a disability under the category of "Other Health Impaired." This was important, because this change meant that a diagnosis of ADHD could qualify a student for accommodations in the regular classroom or in some cases for special education programs "solely on the basis of the disorder." Also, it was interpreted as directing public schools to establish "procedures for locating, identifying and evaluating" children with ADHD "regardless of the severity of their disability" and to offer a "full continuum of placement alternatives." This changing perception of ADHD and recognition in educational law was accelerated by the rise of national advocacy groups such as Children and Adults with ADD (CHADD), which mounted media campaigns specifically designed to reduce stigma associated with the ADHD diagnosis and label and to increase access to services by individuals and families affected by ADHD, as recommended by Sartorius (2007) for all mental health disorders. The second example is related to the application of new technology for drug administration. In 2000, another advance in the treatment of ADHD resulted in a reduction of stigma: the development of effective long-acting formulations of stimulants dramatically reduced a visible marker of ADHD (i.e. public administration of stimulant medication in the school setting).

We have suggested that the development of effective CR formulations of the stimulant drugs was one of the most clinically significant developments of the past decade (see Swanson and Volkow 2009). In the 1990s, the use of medication increased dramatically (see Swanson, Lerner and Williams 1995) and the use of IR formulations of the short-acting stimulants (MPH and AMP) required dosing at school. Since these are Schedule II drugs and self-administration is against the law, administration by school staff was required and anecdotal reports indicated that line-ups at noon resulted in some children being embarrassed and teased. The development of effective once-a-day formulations was based on the concept of acute tolerance to MPH, which had been documented in PET studies of intravenous administration to adults (Volkow *et al.* 1995) and in proof-of-principle studies using clinical pharmacokinetic/pharmacodynamic methods to evaluate oral clinical doses of MPH (see Swanson *et al.* 1999) and AMP (see Greenhill *et al.* 2003). These studies suggested that a new first-order (ascending) drug delivery profile would be superior to the usual zero-order (flat) profile that had been assumed to be optimal, and the Osmotic Release Oral System (OROS[®]) technology and the polymer-coated bead technology was applied to achieve a controlled drug delivery from the gastrointestinal tract after a morning dose of medication. Proof-of-product (efficacy) studies were designed to test this application of technology, and the predicted long-duration of actions was documented in laboratory school studies of Concerta[®] (Pelham *et al.* 2001; Swanson *et al.* 2003) and for Adderall XR[®] (McCracken *et al.* 2003). These efficacy trials were followed by standard clinical effectiveness trials that led to the regulatory approval of Concerta[®] and Adderall XR[®] by the US Federal Drug Administration

(FDA). The duration of effectiveness for 8 hours or more was sufficient for once-a-day dosing, and this avoided the need for a mid-day dose at school. The availability of these CR formulations of stimulant medications led to a rapid shift in prescribing practices. As documented by prescription records (see Swanson and Volkow 2009), after several decades of standard clinical practice of administration of multiple daily doses of IR formulations (typically with a noon dose at school under supervision of school personnel), the standard became administration of a morning dose of CR formulations of the stimulant medication. This acceptance in clinical practice provides an example of how findings from the neurosciences can be translated successfully into clinical applications (see Volkow and Swanson 2008 for a summary).

Dimensions of symptom severity

In preparation for the revision process for DSM-V, the APA, WHO, and the National Institute of Mental Health (NIMH) formed a “study group” to consider dimensional approaches for possible use in revision of DSM-IV criteria for future categorical diagnoses. A report of the deliberations has been published (see Helzer *et al.* 2008). Kraemer (2007) described the implications of a general approach that moves from a binary categorical diagnoses in DSM-IV (i.e. positive when a patient is thought to have a disorder and negative otherwise) to an ordinal diagnosis (i.e. by specifying three or more ordered values based on available and clinically relevant information —e.g. symptom counts, symptom duration, or symptom severity; certainty of diagnosis; degree of impairment). Andrews and colleagues (2008) described an epidemiological study of non-psychotic psychiatric symptoms (i.e. mixed anxiety and depression) documented by clinical interview, which created a dimension based on symptom count that is radically skewed in the population since most respondents report no current symptoms and thus have a symptom count of zero. Rather than using a symptom count, Helzer *et al.* (2008) proposed starting dimensionalization at the item level by using a 3-point scale for the assessment of symptom severity based on presence (0 = none, 1 = mild, or 2 = severe) or frequency (0 = never, 1 = sometimes, or 2 = frequent). Hudziak *et al.* (2008) proposed the use of the Child Behavior Checklist (CBCL) to take advantage of norms based on age, sex, and source of rating (informant).

There are many examples in the ADHD literature of using symptom severity measures as dimensional adjuncts to categorical diagnosis. Conners *et al.* (1969) developed the Hyperactivity Index before the modern era of symptom lists initiated by DSM-III (APA 1980). Swanson *et al.* (1983) used the DSM-III items to develop the Swanson, Nolan, and Pelham (SNAP III) rating scale. Soon after the DSM-IV revisions, several ADHD symptom rating scales were developed, including the SNAP IV (Swanson 1992), the Vanderbilt Rating Scale (Wolraich *et al.* 1996), the DuPaul Rating Scale (DuPaul *et al.* 1998), and the Disruptive Behavior Disorders Rating Scale (Molina *et al.* 1998). All of these scales use a 4-point scale for symptom severity (e.g. not at all or never = 0; just a little or infrequently = 1; quite a bit or often = 2; very much or very often = 3). Collett and colleagues (2003) provided a thorough review of the psychometric properties of these “narrow band” approaches. They all show rather low correlations for parent and teacher ratings (about 0.3), but other psychometric properties of rating scales (test-retest reliability, validity, etc.) are adequate and about the

same for all of these instruments. However, other psychometric properties may impose a serious threat to the use of these norms.

For both parent and teacher completed rating scales, the age and sex norms are typically based on the T-score (i.e. a transformation of the z-score with a mean of 50 and a standard deviation of 10), which assumes a normal distribution. Deriving T-scores from data based on a skewed distribution violates one of the basic assumptions for calculating a standard score, and the use of a T-score cut-off is not recommended by some (see Powers *et al.* 1998 for the DuPaul ADHD rating scale, and Swanson *et al.* 2000 for the SNAP). Others recommend the use of T-scores, but with torturous provisions made in an attempt to adjust for skewness (see Achenbach and Rescorla 2001). The skewed distributions for the CBCL and SNAP IV are shown in Figure 20.3.

There are many neuroethical issues related to the approach of using a dimension of symptom severity, and we will consider two here: *statistical appropriateness of norms* and *arbitrary setting of cut-offs*.

Using an ADHD dimension of symptom severity may result in overestimation of statistically extreme cases due to the skewness of the distribution of scores in the population norms. For example, in a population sample of 875 school-aged children, the z-score cut-off of 1.65 SD units (expected to identify 5% as extreme) actually identify 8.4%, representing overestimation by a factor of 1.7 (see Swanson *et al.* 2000; Wigal *et al.* submitted; and <http://www.ADHD.net>). The neuroethics of using a procedure known to have a serious flaw has not been discussed in the literature but should be.

Another neuroethical issue is where to place the cut-offs for the specification of threshold and subthreshold cases. Some have suggested that impairment be used to set the cut-off on the dimension of symptom severity (see Haslam *et al.* 2006). Helzer *et al.* (2008) recommended the use of a statistical approach to determine the threshold that matches the percentage of cases identified by the categorical diagnosis. For this purpose, some ADHD

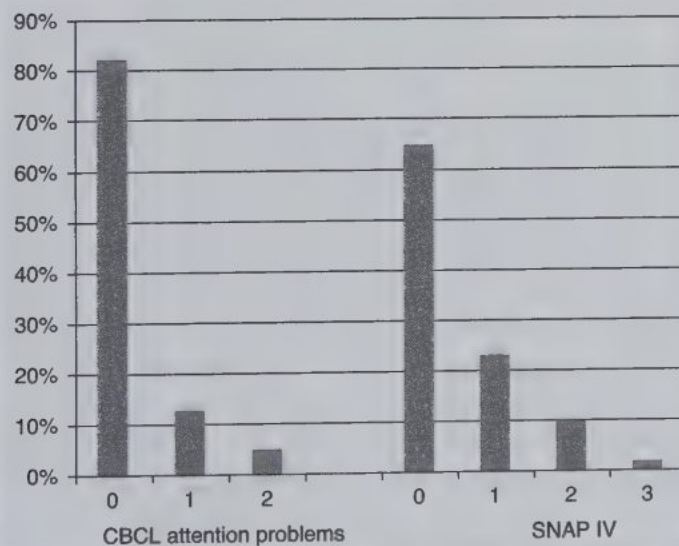


FIG. 20.3 Dimension of symptom severity.

studies have suggested that teacher ratings are superior to the parent ratings when evaluated relative to the gold standard of categorical diagnosis (see Power *et al.* 1998; Tripp *et al.* 2006). However, if the main purpose of the dimensional approach is to offer an alternative to the categorical approach, then all of these procedures may minimize the added value of the dimensional approach.

Continuum of behavior

Instead of using all negative items describing symptoms of a disorder (as in the SNAP) or problem behaviors (as in the CBCL), some items on the rating scales have been worded to be positive in order to represent the opposite of symptoms. A prime example of this approach is provided by the Strengths and Difficulties Questionnaire (SDQ) (Goodman 1997). The SDQ has 25 items, and some are worded to reflect strengths and others to reflect difficulties (but no item has both extremes). The Difficulties are rated on a 3-point scale (0 = "not true"; 1 = "somewhat true"; or 2 = "certainly true") and the Strengths are rated on a reversed 3-point scale (2 = "not true"; 1 = "somewhat true"; and 0 = "certainly true").

In the SDQ, there are five subscales each with five items, and the number of items worded to reflect strengths and difficulties varies across the subscales. The SDQ Hyperactivity–Inattention subscale lists three Difficulties ("restless, overactive, cannot stay still for long"; "constantly fidgeting or squirming"; "easily distracted, concentration wanders") and two Strengths ("thinks things out before acting" and "sees tasks through to the end, good attention span"). The scoring of Strengths is reversed compared to Weaknesses (see earlier), so the scores of all items vary from 0 (Strengths) to 2 (Weaknesses). The range of the Hyperactivity–Inattention subscale is 0 to 10, with a score of 0 indicating extreme lack of difficulties (i.e. good attention) and a 10 indicating and extreme presence of difficulties (i.e. poor attention or "attention deficit"). Unidirectional wording (i.e. either as a Strength or a Weakness, but not both) and "reversed scoring" of items reflecting Strengths (2 to 0) compared to Weaknesses (0 to 2) are used. The distribution of the SDQ Hyperactivity–Inattention subscale is highly skewed (see Figure 20.4). However, the SDQ Total Score serves as a dimensional measure of risk for psychiatric diagnosis across the range of behavior (Goodman and Goodman 2009).

Swanson *et al.* (2000, 2002) developed the Strengths and Weaknesses of ADHD-symptoms and Normal-behavior (SWAN) rating scale. The dimensionalization of the SWAN starts at the item level, but instead of considering each DSM-IV item as a symptom (as suggested by Helzer *et al.* 2008), each item was considered to cover the manifestation of behavior across the full range in the population. The DSM-IV top-down approach was taken to maintain correspondence to clinical observation, so the content remained the same, but each item was re-stated to be neutral, with an average (0) serving as an anchor that would be subjectively defined by the respondent. The same severity scale as the SNAP was used for the range of weaknesses (i.e. problem behavior that may reach the criteria for symptom presence: +1, +2, and +3), but the opposite was used for the range of strengths (i.e. -1, -2, and -3). The distribution of the SWAN is near normal in population samples (Swanson *et al.* 2002; Hay *et al.* 2005; Poderman *et al.* 2008). Figure 20.4 contrasts the behavioral continuum for the SWAN ratings of behaviors with those of the SDQ. The SDQ has a skewed distribution in the population norms, but the full range of scores at the item level on the SWAN produces a near-normal distribution in the population.

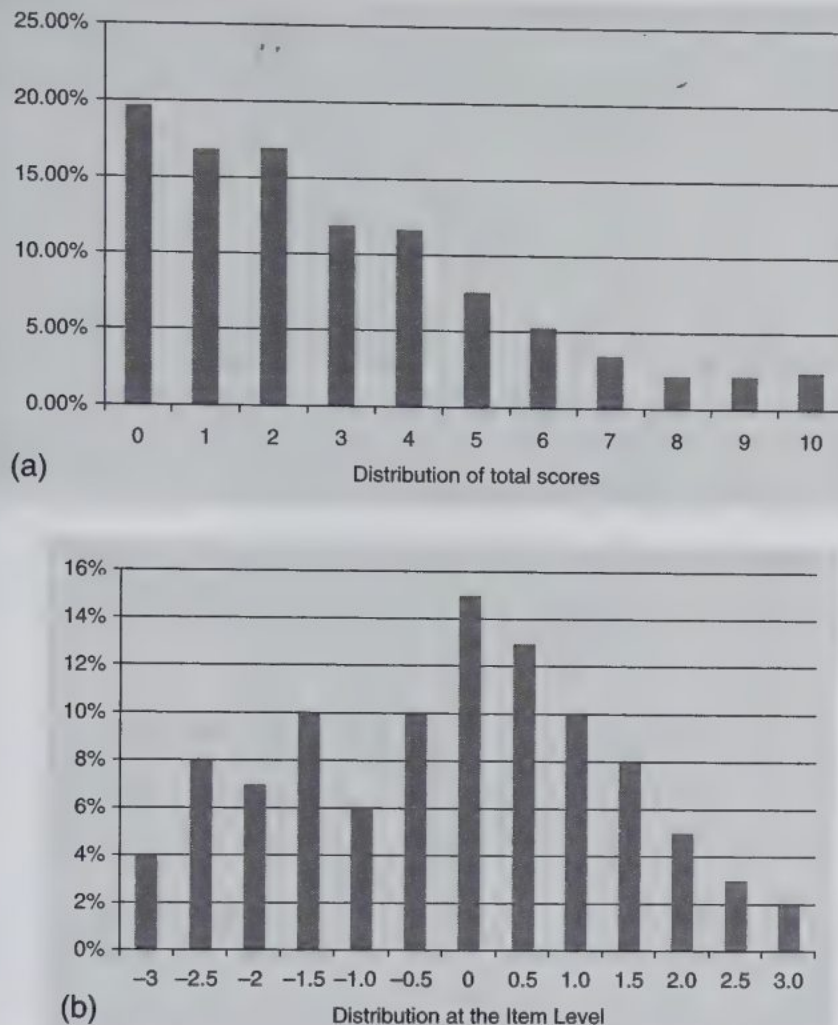


FIG. 20.4 a) Distribution of SDQ hyperactivity/inattention scale in the population. b) Distribution of the SWAN in the population.

What are the ethical issues about establishing cut-offs for the SDQ and SWAN? We will discuss two here. First, the norms provided in the SDQ manual (<http://www.SDQ.com>) are not based on discrete cut-off values, but instead specify a band of scores to designate abnormal behavior. However, the distribution of the Hyperactivity -- Inattention subscale is highly skewed, so any cut-off based on the distribution would suffer from the same statistical flaw that affects a z-score or T-score cut-off. Several large population studies have verified that the distribution of summary ratings on the SWAN is a near-normal distribution (e.g. see Swanson *et al.* 2002; Poderman *et al.* 2007). Second, Jablensky (2005) suggested that the critical issue is the separation of psychiatric disorder from normality, and the categorical approach is based on this at both the item level (presence or absence of symptom) and the symptom count level (exceeding a threshold set by policy). Even though subjective, these decisions provide information regarding psychopathology based on clinical wisdom expressed as policy by the DSM-IV and ICD-10 criteria. This clinical wisdom is not utilized

by the continuum approach. To set the cut-off on the normally distributed dimension of behavior, it would be necessary to evaluate separately impairment and the need for treatment, as is common in other fields of medicine (e.g. for the dimension of blood pressure and the categorical diagnosis of hypertension)

Summary

The three approaches for defining a spectrum of ADHD generate different distributions of scores in the population (see Figure 20.5). We have discussed some neuroethical issues related to each approach. For the categorical diagnosis, we discussed the profound impact of a top-down policy that sets decision rules and cut-offs, and the impact of cut-offs on stigma and access to services. For the dimension of symptom severity, we discussed a flaw in norms based on population distributions that are non-normal, and the statistical deceptiveness of cut-offs established on them. For the continuum of behavior, we discussed the arbitrariness of cut-off values, the lack of an anchor for the distinction between normal and abnormal, and the need for concurrent assessment of impairment.

TREATMENT WITH STIMULANT MEDICATION AND THE ADHD SPECTRUM

In clinical practice, both the categorical diagnosis of ADHD and HKD are taken as indications for treatment with stimulant medication. The implications related to the use of the three approaches of defining an ADHD spectrum for the measurement and interpretation of response to stimulant medication will be addressed in this section.

Categorical diagnosis and response to stimulant medication

It is clear that the large difference in administrative prevalence of the ADHD and HKD categorical diagnoses (see Figure 20.2) has a major impact on treatment. In North America, the first-line treatment for the multiple subtypes of ADHD diagnosed by DSM-IV is with stimulant medication (see NIH Consensus Conference on ADHD 1998), while in European and other countries stimulant medication is recommended as the first-line treatment of only severe ADHD or HKD, which is described earlier and in the literature on clinical practice, such as by the National Institute of Health and Clinical Excellence (NICE) in its recent guidelines on ADHD (NICE 2008).

The historical and cultural differences associated with the acceptance and use of different diagnostic systems (i.e. DSM-IV and ICD-10) creates very large cross-national differences in the use of stimulant medication, which is documented by records of national consumption of stimulants (see United Nations Office on Drugs and Crime 2008) and by databases of prescription records and clinical practices (see Zito *et al.* 2003). These differences in rates of use of stimulants are primarily due to high rates in North American (especially the US)

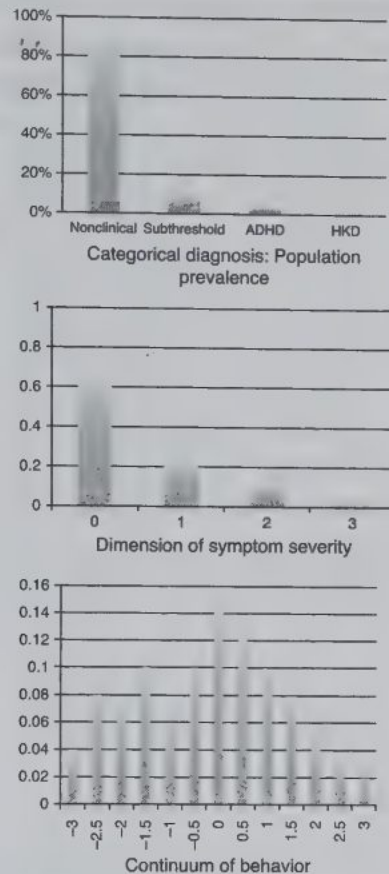


FIG. 20.5 Three approaches for defining an ADHD spectrum.

compared to other geographic regions. For example, the most recent 2008 United Nations (UN) report on national consumption of the most commonly used stimulant medication, methylphenidate (MPH), states that in the past 3 years "... the United States has accounted for 77 percent of the calculated worldwide use of the substance" (UN 2008). This dramatic difference appears to be a direct consequence of policies for making categorical diagnoses.

These cross-national differences have been noted for decades. For example, Taylor (1979) observed that despite the similarities in epidemiologic prevalence of ADHD in different counties, stimulant medications "... are used with frighteningly different frequency in different places." For example, Swanson and Volkow (2009) concluded that, despite recent increases in both the US and UK, the cross-national difference is still substantial. They used the UN estimates of national consumption (expressed as defined daily dose per 1000 inhabitants per day) to compare the use of stimulants in the US and UK from 1996–2005. In 2005, the defined daily dose was 1.33 in the UK versus 17.83 in the US—a 13.4-fold difference. Jick and colleagues (2004) provided similar national estimates based on the UK General Practice Research Database for the UK (where less than 1% of children are recognized and treated) and HMO databases in the US (where about 10% of children are recognized and treated with stimulants).

When used at a relatively high rate, as is the custom in the US, what is the evidence of benefit? The MTA provides some information about short-term response based of initial titration (see Greenhill *et al.* 1996), but a main purpose was to provide information about long-term response, defined operationally as more than one year. When categorical diagnosis is used as an outcome measure for the MTA, the assessments reveal that 22% of the MedMgt group and 18% for the Comb group no longer met the DSM-IV criteria for ADHD Combined type compared to 41% in the Beh group and 42% in the CC group. Latent class analysis of the 3-year and 8-year outcomes suggested that the relative benefit of medication was superimposed on a large general trend of reduction of symptoms in most cases, which was independent of medication use and was maintained over time in some but not in others (see Swanson *et al.* 2007).

The treatment of children with ADHD and HKD with stimulant medication is not usually evaluated by re-evaluation of the criteria for categorical diagnosis. For example, the overall goal of this treatment in the MTA was not just to reduce symptom presence to below threshold for diagnosis. Instead, an upward adjustment of dose of medication was initiated if the treating clinician considered there was "room for improvement," which was quantified by dimensional ratings of symptom severity using the SNAP and other rating scales.

Dimension of symptom severity and response to stimulant medication

In the MTA, the primary outcome measures of the large assessment battery were ratings of symptom severity on the SNAP rating scale completed by parents and teachers (see MTA Group 1999). Relative benefits of stimulant medication on the subscale scores of Inattention and Hyperactivity/Impulsivity were documented at the end of the 14-month treatment-by-protocol phase by comparison of the MedMgt and Comb groups (whose assigned treatment included the MTA medication algorithm) to the Beh and CC groups (whose assigned treatment did not).

Santosh *et al.* (2005) provided an empirical basis for the selective treatment of children with diagnosis of HKD using the symptom severity ratings on the SNAP. In their re-analysis of the MTA, the subgroup of ADHD-Combined cases that met the ICD-10 criteria for a diagnosis of HKD (145 out of the 579 participants) showed a larger beneficial effect of the MedMgt condition compared to the Beh condition (effect size approximately 1.0) than the remaining subgroup that did not meet the HKD criteria (effect size approximately 0.5). However, the benefit to the latter group was also significant and large, providing an empirical basis for treatment of the less severe as well as the severe ADHD cases.

Swanson *et al.* (2001) proposed the use of a summary measure of the dimension of symptom severity established by averaging the SNAP ratings across domains (symptoms ratings of Inattention and Hyperactivity/Impulsivity) and sources (parents and teachers). This reduced the group variances as expected by the Spearman-Brown principles and increased effect size (see Swanson *et al.* 2001). The use of this dimensional measure of response to treatment allows for evaluation of improvement beyond the symptom count criteria of categorical diagnosis. In the MTA, the groups treated with the medication algorithm (MedMgt and Comb) showed a larger reduction in symptom severity, with individual cases moving from a high level of symptom presence (a rating of "pretty much" = 2 or

“very much” = 3) to a low level of symptom presence not considered to represent psychopathology (“just a little” = 1) or symptom absence (“not at all” = 0). Rather than using a symptom count of categorical diagnosis, the measure of “remission” was a dimensional measure—the summary score on the SNAP ≤ 1.0 . For this dimensional measure, 68% of the Comb, 56% of the MedMgt, and 34% of the Beh individuals showed an “excellent response.”

The neuroethics of measures and characterizing response to stimulant medication is complex. This has been addressed in a summary of findings of the MTA (see Swanson *et al.* 2008). There is no clear consensus about the meaning of the measure of long-term response based on the symptom severity dimension, which was large at the 14-month assessment but dissipated and disappeared by the 3-year assessment. The confusion about the MTA outcomes has been controversial, and public reports may have been misinterpreted (see *Kids on Pills* 2010). Without an untreated control group, the lack of relative superiority of the MedMgt or Comb conditions over the positive control groups (Beh and CC) does not necessarily imply a lack of effectiveness, since all groups improved over time and the treatments converged after the treatment-by-protocol phase of the randomized control trial (RCT).

Continuum of behavior and response to stimulant medication

Recently, the SWAN was used as a measure of response to stimulant medication by Acosta *et al.* (2009) and by Arcos-Burgos *et al.* (2010). Based on latent class analysis, they used the extended range of the SWAN to form subgroups with and without high levels of hyperactive/impulsive behavior, and then they contrasted the subgroups when rated on the SWAN both on and off medication. The SWAN extended the range of measurable response, which for the dimension of symptom severity (i.e. SNAP ratings) has a minimum of 0 but for the continuum of behavior (i.e. SWAN ratings) has a minimum of -3.0 .

The neuroethics of measuring response beyond the presence of psychopathology is related to the fundamental clinical rationale for the clinical use of stimulant medication—to reduce distress and impairment associated with the presence of symptoms of ADHD and HKD (i.e. the diagnostic criteria of DSM-IV and ICD-10). Response to stimulant medication can go beyond the reduction of symptoms and may produce enhancement of non-symptom behavior. If, normal behavior (and individuals) as well as abnormal behavior (and individuals) is responsive to stimulants then, this may question the implicit clinical requirement that treatment “corrects a deficit.” This requirement operates to restrict the use of stimulants to medical use for the treatment of ADHD, but this may need to be questioned in the face of frequent use for enhancement that is illegal based on this policy (see Sahakian and Morein-Zamir 2007).

TREATMENT ISSUES AND NEUROETHICS

Some neuroethical issues transcend the three spectrum approaches discussed previously. We will discuss five here: the prevalence of medication use for the treatment of ADHD that

has continued to increase linearly for decades; the use of favorable response to medication to confirm the diagnoses of ADHD and HKD; the non-medical use of stimulants with the expectation of cognitive enhancement that is becoming common in some settings, such as college; the lack of evidence of long-term relative benefits of stimulant treatment over other treatments; the risk for non-medical use to escalate into abuse in vulnerable individuals in the population.

Prevalence of use of stimulant medication

The changing diagnostic criteria for ADHD may be contributing to a persistent trend in the US for the regular increase in prescription of stimulant medications for ADHD (see Safer and Krager 1985; Safer *et al.* 1996; Zito *et al.* 2003). An acceleration of this was noticed two decades ago (Swanson *et al.* 1995), and it was suggested that this trend was due to correction of under-recognition and undertreatment of children compared to the estimated prevalence of ADHD according to the DSM-IV criteria and decision rules just adopted and being implemented at the time. It was predicted that at some point it would asymptote, but by 2005 the treatment rate was so high it exceeded the traditional 5% estimate of population prevalence (i.e. 9.3% of 12 year old boys and 3.7% of 11 year old girls; see Bloom and Cohen 2007). But, so far this linear increase has continued and an asymptote has not been reached. Swanson and Volkow (2008) suggested that recent increases in supply may be increasing more rapidly than the prescriptions for stimulants.

The proposed DSM-V revisions, including the increase of age of onset from 7 to 12 years of age, the addition of symptoms of impulsivity, and the reduction of cut-off for adult diagnoses (see www.apa.org), are likely to increase the recognition rate and thus the treatment rate in the future. Theoretically, if the diagnosis of ADHD is restricted to a minority of the population and the use of medication is restricted to clinical cases, then at some point an asymptote for the recognition and treatment rates should occur.

Use of response to medication to confirm diagnosis

The fundamental rationale for the clinical use of stimulant medication is to reduce distress and impairment associated with the presence of symptoms of ADHD and HKD (i.e. the diagnostic criteria of DSM-IV and ICD-10). One strategy to confirm a diagnosis has been response to treatment. This may be problematic if, as discussed above, the direction of response (improvement) is used alone to define benefit, since many individuals who do not meet the strict criteria for a diagnosis of ADHD also may show the same direction of response (see Rapoport *et al.* 1978). In addition to direction of response, the correction of a deficit may be used to limit those considered to benefit from treatment with medication. However, the responses to medication based on these dual criteria—improvement and correction of deficit—are dependent on setting an appropriate cut-off for defining the deficit. If the diagnostic cut-off is set low so that impairment is not present, then response to medication may not move an individual from an impaired to a non-impaired state. The extreme would exist when an individual is unimpaired (normal) and medication is used to enhance a non-impaired state.

The correction of a deficit may be conceptualized in different ways for the three diagnostic approaches. For the categorical diagnosis approach, the individual may fall well below the threshold for criterion symptoms, but may include non-criterion symptoms that create distress or dysfunction. For the dimension of symptom severity, an individual may fall below the cut-off for presence of psychopathology, but may seek enhancement to a superior level of functioning. If the dimension does not measure beyond the absence of psychopathology, then movement on the dimension beyond zero would not be evaluated. However, if the continuum approach is used for the same individuals, then, movement across the full range can be measured (see Arcos-Burgos *et al.* 2010).

Non-medical use of stimulants for cognitive enhancement

It is clear that the non-medical use of stimulant drugs has been increasing (McCabe 2006, 2007a), and that the primary reason for this use is the expectation of enhancement in educational and workplace settings (see McCabe *et al.* 2007b). Apparently, non-medical use may occur in 30% of college students (see Wilens *et al.* 2008 for a review), and if so it may even exceed the medical use for the treatment of ADHD (see Swanson and Volkow 2008).

The non-medical use of stimulant medication has been revived as a topic of debate (see Sahakian and Morein-Zamir 2007), and this has generated controversy and discussion of important neuroethical issues in the scientific literature (see Volkow and Swanson 2008) and in the popular press (see Stix 2009). In the context of modern society, the widespread non-medical use of highly regulated stimulant drugs (i.e. Schedule II in the US) is occurring, especially by high school and college students who expect that this will improve academic productivity and performance (see McCabe *et al.* 2007b). The legal issues surrounding the use of a controlled substance are serious; the use of a Schedule II drug without a prescription is technically or legally a felony. Therefore, this is an important neuroethical issue that needs to be addressed.

Greely *et al.* (2008) defined an agenda for the discussion of neuroethical concerns in three areas: safety and risk of unintended side effects; freedom from coercion to enhance by legal or other means; fairness of use in competitive situations and unequal access to cognitive enhancers. They also proposed four mechanisms to shape evidence-based policy in this controversial area: accelerated research on the effects of stimulant drugs on individuals without ADHD to clearly answer questions about potential benefits and associated risks; participation of professional organizations to set guidelines for physicians, educators, and others who interact with individuals who are using stimulants with the expectation of cognitive enhancement; education to disseminate public-health information about the non-medical use of stimulants; and legislative action to bring existing laws into line with norms of modern society.

Specific use for cognitive enhancement has been addressed in a special issue of the journal, *Psychopharmacology* (see Robbins 2009). The use of stimulants in sport practice, either for training or in competition, is banned in the name of fairness and safety (Avois 2006). Their use in the military is sometimes required in some settings when endurance and wakefulness are necessary. The use by professionals, who keep long hours, such as medical residents, has been addressed by Bray *et al.* (2004). One approach to the understanding of the effects of arousal on different tasks and across types of individuals and settings is the

Yerkes–Dodson law (see Arnsten 1998), which historically has been misapplied and even discredited (see Diamond *et al.* 2008). Recently, findings from PET imaging studies (e.g. see Volkow *et al.* 2008a) have suggested that the measurement of local brain activation may offer a way to revive this once discredited approach. We documented that compared to placebo: MPH significantly reduced the task-related increase in glucose by 50%. The stimulant-related focusing of regional brain activation during task performance may be beneficial when neuronal resources are diverted away from the task, perhaps by default mode interference that results in mind-wandering or lapse in attention (see Volkow *et al.* 2006). However, these medication effects could be detrimental when brain activity is already optimally focused. This could explain why stimulants have beneficial effects in some individuals and contexts and detrimental effects in others, generating U-shaped relationships between cognitive performance and dose of medication (Arnsten, 2008).

Long-term outcomes

The MTA was designed to evaluate long-term benefits of treatment with stimulants, either as residual effects after cessation of childhood treatment or chronic effects of continued treatment into adolescence and adulthood. The gold standard for evaluation is the RCT, in which individuals are randomly assigned to treatments with or without medication as a component, to avoid selection bias that might distort long-term medication effects. MTA treatment-by-protocol in the assigned groups was maintained in most cases through the 14-month follow-up. The initial findings at the end of the treatment-by-protocol phase (MTA Cooperative Group 1999a,b) clearly show the relative superiority of assignment to the MTA medication algorithm, and thus confirmed the initial short-term benefits of stimulant treatment documented in the titration trial and extended the evidence of superiority into the long term (defined operationally as more than one year). The findings from the first follow-up, 10 months after the end of treatment-by-protocol, revealed partial loss of the superiority of assignment to the MTA medication algorithm (MTA Group 2004), and the second follow-up revealed the complete loss of the relative superiority (Jensen *et al.* 2007; Swanson *et al.* 2007b; Molina *et al.* 2008) at the assessment 36 months after baseline and 2 years after the end of the treatment-by-protocol phase. This suggests that the superiority of assignment to intensive, carefully monitored medication management (i.e. to the MTA medication algorithm) eventually dissipates completely when the children are returned to community treatment. The relative benefits were not apparent even when compared to children who are never treated with stimulant medication.

This creates a potential neuroethical question: if stimulant medication provides short-term but not long-term benefits, should it be prescribed on the basis of short-term effects? The degree of risk associated with stimulant treatment must be weighed against what is known about potential benefits (including how long they will last),

Risks of abuse

One controversial neuroethical issue is whether treatment with stimulant medications in childhood protects against or increases risk for substance use in adolescence or adulthood.

Initial studies that showed large protective effects (see Wilens *et al.* 2003) have been contradicted by longer follow-up (Biederman *et al.* 2008). This has been discussed by us elsewhere (Volkow and Swanson 2009). These issues were addressed in the follow-up of the MTA study (Molina *et al.* 2007 and 2008), which suggested that childhood treatment does not affect risk—either by increasing or decreasing it.

However, the risk for escalation of stimulants from use to misuse or abuse (see Volkow and Swanson 2003) may be different for the non-medical use of stimulants than for medical use (see Rasmussen 2008). About 20% of the general (non-ADHD) users of stimulants, for example in the non-medical use by the military (in World War II) or in eras of lax regulatory control (in the 1960s and 1970s), escalated to dependence and abuse (see Rasmussen 2008). These questions about risk are still unresolved and require more careful evaluation.

SUMMARY

We present here three approaches for defining a spectrum of ADHD: categorical diagnosis based on symptom counts with subtypes and comorbidities; dimensions of symptom severity based on rating scales with content defined by official manuals; and continuum of behavior based on the full range of behavior that underlies the symptoms.

For categorical diagnoses, there is a profound impact of a top-down policy that sets decision rules and cut-offs, which produces dramatic cross-national differences in recognition and treatment (e.g. of ADHD in the US and HKD in the UK). We discussed the two sides to this issue, with stigma increasing with the use of lax categorical criteria and widespread labeling of children versus access to services decreasing with the use of strict categorical criteria that limit the diagnosis to the most severe cases. Since categorical diagnosis varies so much in different countries, cross-national studies of stigma and services would be an important topic to address to understand further the neuroethics of this difference. For the dimension of symptom severity, the population distributions of ADHD ratings are non-normal, as are symptom severity ratings for other disorders if they occur rarely in the population. We discussed a possible fatal flaw in norms based on some statistical properties of cut-offs based on these distributions. The use of these methods may be inappropriate and possibly deceptive (with respect to a statistical prevalence higher than assumed at any cut-off chosen), which may be a neuroethical issue to be addressed by professions that use rating scales for clinical purposes (e.g. by psychologists who are involved in the assessment of ADHD). For the continuum of behavior, the distribution of ratings is near-normal for the population. We discussed the arbitrariness of cut-off values for a continuum without any natural breakpoints, as well as without a build-in subjective anchor for the distinction between normal and abnormal. For the use of the continuum approach, there may be an increased need for concurrent assessment of impairment.

In summary, consideration of a multiple ways to consider ADHD as a spectrum disorder can contribute to discussions of the neuroethics of this controversial treatment by defining issues about stigma and services, by identifying possible unrecognized problems with the use of statistical norms that may encourage overdiagnosis, and by recommending the assessment of psychopathology based on evaluation of impairment along with evaluation of the underlying behavior that has no well-defined cut-off.

Perhaps the most obvious neuroethical issue we addressed here is about the expectation of cognitive enhancement and the resulting widespread non-medical use of stimulant medication (see Sahakian and Morein-Zamir 2007). We considered the opposing sides taken in the debate about the non-medical use of stimulant drugs and a variety of neuroethical issues in this debate (see Greely *et al.* 2008; Swanson and Volkow 2008; Volkow and Swanson 2008; Stix 2009), but the clearest conclusion might be that current scientific knowledge is inadequate to claim the presence or absence (or degree) of cognitive enhancement in non-medical use of stimulant medications.

The evaluation of long-term benefits of childhood treatment has been addressed the MTA study, which shows that the initial relative benefits of treatments that include stimulants (compared to those that do not) dissipate by 3 years after initiation of treatment (see Swanson *et al.* 2009). The claims of long-term benefits by reducing substance use and abuse have not been supported as the follow-up sample entered adulthood (see Biederman *et al.* 2008). These issues were addressed in the follow-up of the MTA (Molina *et al.* 2007 and 2008), which suggested that childhood treatment does not affect risk for substance use or abuse—either by increasing or decreasing it.

However, the risk for escalation of stimulants from use to misuse or abuse (see Volkow and Swanson 2003) may be different for the non-medical use of stimulants than for medical use (see Rasmussen 2008). About 20% of the general (non-ADHD) users of stimulants, for example, in the non-medical use by the military (in World War II) or in eras of lax regulatory control (in the 1960s and 1970s), escalated to dependence and abuse (see Rasmussen 2008). These questions about the non-medical use of stimulants and the risk of addiction to drugs are still unresolved and require more careful evaluation.

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