ADHD: Subtyping is Revisited

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Abstract

The current ADHD with its diagnostic criteria and subtypes in DSM-5 seems not to be homogenous but heterogeneous with two distinct and unrelated subtypes of "inattention" and "hyperactivity/impulsivity". Unfortunately, the majority of research samples in the literature are of combined subtype that is ill defined and usually is not consisted of 6 symptoms of either subtypes as required by DSM5, but some of the symptoms of each, in a mixed and arbitrary construct. Hence the literature and research have been very inconclusive over ADHD in all aspects. There are vast evidence and facts that ADHD of hyperactive-impulsive subtype is quite distinct from the inattentive subtype in every aspect of symptomatology, clinical course and outcomes, neuro-psychologically, neuro-biologically, genetically and in response to treatment, so they should not be under the same disease category.

Method: A selective review of the literature with the focus on the differentiation between the current subtypes of ADHD, "predominantly inattentive" (ADHD-I) and "predominantly hyperactive-impulsive" (ADHD-HI) were conducted. In probing on the difference between the two subtypes of ADHD, the research on the underlying pathophysiology and neurobiology of the subtypes were specifically reviewed to differentiate the difference beyond the descriptive and symptomatic level.

Keywords: ADHD; DSM5; Hyperactive-Impulsive (ADHD-HI); Inattentive (ADHD-I)

Introduction

The literature on pathophysiology of ADHD is quite inconsistent with mixed results to synthesize all the findings in any domain of neuropsychological, neuroanatomical, neurochemical or genetics to link them to the correspondent clinical phenotypes of the current ADHD subtypes. On a descriptive level, the symptomatology of two distinct ADHD subtypes of hyperactive-impulsive (ADHD-HI) and inattentive (ADHD-I) are quite different and hardly seem to come under the same disease entity as it has long been categorized by DSM classifications with no change in the recent DSM5 [1]. While ADHD-I or ADD as it was labeled in the past, it is an "attention-deficit" disorder, ADHD-HI beyond an attention-deficit disorder, it is a behavioural disorder with cardinal symptoms of hyperactivity, impulsivity and behavioural disinhibition [2-3]. As a result, the majority of research samples, hence the conclusions of the literature for clinical practice have relied heavily on the "combined subtype" that is an ill-defined combination of both subtypes. This ill-defined combined subtype usually is not consisted of 6 symptoms of either subtypes as required by DSM5, but some of the symptoms of each, in a mixed and arbitrary construct with no clear underlying pathophysiology as either subtypes. This contradicting fact has long caused an intense argument in the literature on the total validity of ADHD as a homogenous or single disorder with a single pathophysiology or two or more heterogeneous disorders with different pathophysiology [5,6], that I will attempt to review and explore in this paper.

ADHD: Homogenous or Heterogeneous?

In fact throughout the history, ADHD has been a homogeneous condition, first described as "hyperkinetic" or "hyperactive" syndrome or disorder of children, with recognition of "impulsivity" as a component of hyperactivity first by Laufer., *et al.* [7] in 1957. The second edition of DSM, i.e. DSM-II in 1968 [8] published by the APA, that for the first time recognized the condition as a disorder, labeled it as "hyperkinetic reaction of children". It was not until the third edition of DSM [9] in 1980 that recognized the condition as an attention deficit with hyperactivity and labeled it as such, i.e. ADHD, that we started facing a combined and heterogeneous disorder. Unfortunately, since then the research samples have been mostly undifferentiated or of combined subtype with rare comparison between the two subtypes, so to clarify any distinctions between the two if any.

The few available comparison studies between the subtypes have shown that there is a distinct difference between the two with the conclusion of the most that ADHD is a heterogeneous condition with differences not only in symptomatology and the course of illnesses across the brain development, but differences in cognitive functions and different etiopathophysiology [10-11]. Goth-Owens., *et al.* [12] in their comparison study of 572 children and adolescents with pure inattentive subtype (ADD), combined type (ADHD-C) and non-ADHD controls, reported slower cognitive interference speed in the ADD vs. ADHD-C and controls comparisons. A similar result was reported by Carr., *et al.* [13] who reported an attenuated attentional blink versus controls and ADHD-combined addressed in a sample of 145 ADD/ADHD and typically developing comparison adolescents (aged 13 - 17). A similar result has been reported by Solanto., *et al.* [14] that predominantly inattentive subtype shows worse performance than combined subtype and control groups on the WISC-III Processing Speed Index. This has made some researchers to question the validity of DSM current diagnostic criteria of ADHD to include two distinct subtypes of inattentive and hyperactive/impulsive under the same diagnostic umbrella [16]. Martel., *et al.* [15] in comparison between the two subtypes, reported "a composite executive function factor was significantly related to inattentive but not hyperactive-impulsive symptoms". The authors concluded "Executive function weakness in adolescent ADHD is specifically related to symptoms of inattention-disorganization". Nigg., *et al.* [16] also reported that symptoms of inattention-disorganization were uniquely related to executive functioning when hyperactivity-impulsivity controlled. "Inattention was associated with slower response speed, and hyperactivity-impulsivity with faster output speed. Results were not accounted for by IQ, age, gender, education level, or comorbid disorders". Also Marshal., *et al.* [18] found academic underachievement in a group of 6 - 12 years old with ADHD without hyperactivity. Friedman., *et al.* [17] have reported that such cognitive deficits continue until late adolescence.

The extension and probably progression of the cognitive deficit and poor academic performance across life span in the inattentive subtype is in contrast with the improvement of cognition and even some of the behavioral profiles in the hyperactive-impulsive subtype. Faraone., *et al.* [18] in their meta-analysis show that prevalence of ADHD declines with increasing age, and in a better word, many subjects grow out of the illness, or the severity changes for the better. Lara., *et al.* [19] using data from the World Health Organization World Mental Health Surveys report that 50% of childhood ADHD does not persist to adulthood. Kessler., *et al.* [20] in their recent report on the prevalence and correlates of adult ADHD in the United States, though in a mixed sample of subtypes, report that 85% of the affected population have high school education or beyond, with 35% up to 15 years and 15.8% over 16 years of high education. In this population of adult ADHD in US, 72% were employed and functional with half of them earning above average income,45% currently married and 17.7% previously married. Although many of these studies and comparison between the ADHD subtypes, have been between the inattentive and the combined subtype, not purely hyperactive/impulsive subtype, the recent meta-analytic review of prevalence studies by Wilcutt [21] has clarified some of these confusions and doubts. In this meta-analytic review of 86 studies of children and adolescents (N = 163,688) and 11 studies of adults (N = 14,112), the prevalence of ADHD changes from 10.5% in pre-school age group down to 11.4% among 6-12 years old to 8% in adolescents and 5% in adults. The subtype symptoms group also change, but with significant improvement in ADHD-HI, from 4.9% in 2 - 3 years old down to 2.9% in 6 - 12 years old, down to 1.1% in adolescence and remains the same in adults. But in sharp contrast, the prevalence of ADHD-I rises from 2.2% in preschoolers to 5.1% in 6 - 12 years old and slightly up to 5.7% in adolescents with a decline in adulthood to 2.4%. While in the analysis and report of Wilcutt [21], it seems that the prevalence of ADHD-I is lowering when

reaching adult age, more detailed analysis of the adult studies (available in the supplement table 10 of Wilcutt's report) reveals that majority of samples other than the study by DuPaul., *et al.* [22] which has more ADHD-HI in their sample and Kessler., *et al.* [20] that has no subtype comparison, show a prevalence of > 4% for ADHD-I compared to 1.6% in the ADHD-HI.

From these few studies as examples, we know this much that the hyperactive/impulsive subtype is not only different from the inattentive subtype on phenotypes and clinical manifestations, but in regard with the clinical course and outcomes. Although the ADHD-HI has attention and cognitive deficits as their pathognomonic symptoms, it seems that these are also different from the cognitive deficits in the inattentive subtype.

Wåhlstedt., *et al.* [6] found among four neurocognitive variables (inhibition, working memory, RT variability, delay aversion), only inhibition and RT variability "specifically related to symptoms of inattention" and "none of the neuropsychological measures was primarily related to symptoms of hyperactivity/impulsivity" and ADHD-HI performed superiorly in several measures of executive function. Although ADHD-HI subjects could have deficits in "sustain attention" and get bored easily and fail on such tasks as in the classroom settings, their attentions seem to be selective and they perform better on fast-paced than slow-paced tasks, with the abilities to perform multi-tasking by dividing and switching their attentions between interested tasks [23]. This could explain well the high levels of education, employment, income and IQ among these subjects [24-27].

It has long been reported by the parents that some ADHD children are gifted and have high IQ's; causing controversies among researchers that if such diagnosis is plausible in the presence of high intelligence. Antshel., *et al.* [24] in a group of 49 ADHD children with IQ > 120 showed that such diagnosis is valid and the group met the diagnostic criteria, though ADHD with high IQ seemed to be more familial and running in first degree relatives. De Zeeuw., *et al.* [25] in their diffusion tensor-imaging scan study of 108 children with ADHD with low and high IQ in comparison with 106 typically developing controls, reported while low IQ subjects had a delay in cortical development, the high IQ ADHD children had a stable cortical development, characterized by small, more global reductions in brain volume. Mahone., *et al.* [26] in studying the effects of IQ on executive function (EF) measures in children with ADHD reported that there is poorer discriminatory power for these measures among children with above average IQ. Loureiro., *et al.* [27] have also shown that highly gifted children with ADHD have a particular neuropsychological profile with an important difference (at least 20 points) between verbal IQ and performance IQ at Wechsler Intelligence Scale for Children (WISC III) when compared to highly gifted children without ADHD. This is interesting as the studies on highly gifted children in general have shown such difference between verbal and performance IQ's, while there is no such gap difference among control children [23-27]. Therefore, it seems that the combined subtype group in the follow up comparison studies [24] who outperform the inattentive subtypes are mostly the hyperactive-impulsive group. In the next section, I will attempt to show that the above clinical course and follow up studies are in agreement with the neurobiological studies of ADHD.

The neurobiological studies of ADHD

Sagvolden., *et al.* [28] in their "dynamic developmental theory" have differentiated between the two ADHD subtypes by linking "hypofunctioning mesolimbic and nigrostriatal dopamine" to hyperactivity/impulsivity subtype and "hypofunctioning mesocortical dopamine" to inattentive subtype. These authors hypothesize that a hypofunctioning mesolimbic dopamine branch produces altered reinforcement of behavior and deficient extinction of previously reinforced behavior. This gives rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioral variability, and failure to "inhibit" responses ("disinhibition"). A hypofunctioning mesocortical dopamine branch will cause attention response deficiencies (deficient orienting responses, impaired saccadic eye movements, and poorer attention responses toward a target) and poor behavioral planning (poor executive functions). A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficient non-declarative habit learning and memory. This theory somewhat is in agreement with a long-theorized response or behavioural disinhibition as the core pathophysiological process in ADHD of hyperactive-impulsive subtype.

Long before DSM-III [30] in 1980 to classify ADHD into two main subtypes of ADD with Hyperactivity (ADHD), and ADD without Hyperactivity (ADD) that is still ongoing with minor modification, ADHD had been known as a disorder of attention deficit and hyperactivity in one. Laufer., *et al.* [7] in 1957, soon after the first edition of DSM-I [30] and before the second edition (DSM-II) [8] that labeled

the condition only as "hyperkinetic reaction of children", introduced and added the impulsivity into the condition and labeled it as "Hyperkinetic Impulse Disorder". Later on others, including Douglas in 1972 [31] expanded the phenotype of impulsivity to the disorder of "self regulation", deficiency in modulation of arousal, immediate reinforcement seeking and poor impulse control. Later on Quay in 1988 [32] and Barkley., *et al.* [33] in 1992, hypothesized the "response inhibition" related to frontal lobe dysfunctions as a core pathognomonic phenotype in ADHD-HI. In 1997 Barkley [34] went farther by proposing, "Poor behavioural inhibition is specified as the central deficiency in ADHD". Elsewhere I have expanded the behavioural disinhibition not only as a cognitive deficiency in the form of "response inhibition" but as a general disinhibition in ADHD-HI that causes risk taking behaviours and so many negative consequences, e.g. road rages, accidents, conduct and substance use disorders among these subjects [4]. Recently our research group in a sample of 134 adults have shown the close association of behavioural disinhibition with impulsivity and hyperactivity in ADHD-HI and that this phenotype is not only in cognitive domain but a general disinhibition of behaviours. We have also shown that this behavioural disinhibition is more associated with post-morbid complications of ADHD, e.g. risk taking behaviours, substance use and other conduct disorders than impulsivity or any other phenotypes in ADHD-HI [3].

Along this line, Elkins., *et al.* [35] have reported that hyperactivity/impulsivity predict initiation of all types of substance use, nicotine dependence, and cannabis abuse/dependence, even when controlling for conduct disorder (CD). By contrast, relationships between inattention and substance outcomes disappeared when hyperactivity/impulsivity and CD were controlled for, with the possible exception of nicotine dependence. Carmona., *et al.* [36] in children and adolescents and Scheres., *et al.* [37] have found that ventral striatal activation was negatively correlated with parent-rated hyperactive/impulsive symptoms. These researchers among others related the symptoms of impulsivity/hyperactivity to diminished reward anticipation. Ströhle., *et al.* [38] using functional magnetic resonance imaging (fMRI) have reported that ventral striatal activation in adults with ADHD during gain anticipation was negatively correlated with self-rated symptoms of hyperactivity and impulsivity. Berlin and Bohlin [39] studying the relation among response inhibition, hyperactivity, and conduct problems in a nonclinical sample of 115 preschool children, using 2 different types of go/no-go tasks and a Stroop-like task, reported that hyperactivity and conduct problems were related to disinhibition, and the measures of response inhibition, and not other performance measures. Interestingly, the correlation between response inhibition and conduct problems was not significant when partialling out the effect of hyperactivity, whereas the correlation between inhibition and hyperactivity did remain significant when controlling for conduct problems.

Eisenberg., *et al.* [40] in their pilot study on the genetic risk study of ADHD in 1999 showed " the impulsive-hyperactive type of ADHD (excluding inattention) was associated with the high enzyme activity COMT val allele". COMT (Catechol-O-methyltransferase) is the enzyme that degrades dopamine in the prefrontal cortex with its val allele degrades dopamine faster (four times) than its met allele and has been shown to be more abundant in ADHD-HI than even the normal brains. The Val allele of COMT gene is an evolutionary polymorphism, resulting in a substitution of methionine (Met) for valine (Val) in the COMT enzyme [41]. In the human brain, Met/Met homozygotes having about 40% less COMT activity than Val/Val homozygotes in the prefrontal cortex. The alleles are co-dominant, resulting in Val/Met heterozygotes having an intermediate level of COMT activity. This evidence strongly suggests that Met/Met homozygotes have the highest baseline level of dopamine available in the prefrontal cortex (because dopamine is four times less catabolized) with Val/Met heterozygotes having an intermediate level and Val/Val homozygotes having the lowest level of prefrontal dopamine, as a result of high consumption [42,43].

Eisenberg., *et al.* [40] also recognized such genetic association, i.e. COMT val allele with the increases in CNS dopamine (and norepinephrine) clearance, consistent with the use of methylphenidate that increases dopamine (and norepinephrine) turnover, in the treatment of ADHD. This study perhaps was the first one to show the difference between subtypes of ADHD not only clinically and phenomenologically, but also pathophysiologically and genetically. For the first time, there was an evidence that at least the impulsive-hyperactive subtype of ADHD's brain is not deficient in dopamine or other neurotransmitters, but different [3,4]. Following Eisenberg's group original study,

a few others e.g. Halleland., *et al.* [43] also showed association between COMT haplotypes and hyperactivity/impulsivity symptoms in adults. Paloyelis., *et al.* [44] showed a direct link between the prefrontal cortex (COMT (Val158Met)) and the striatum DAT1 (Dopamine transporter) (10/6)) with discounting rates in a hypothetical task (but not a real-time task) and self-ratings of trait impulsivity in hyperactive/impulsive ADHD subtype. Similar results were later on supported by Malloy-Diniz., *et al.* [45] who have reported association between COMT val158met polymorphism and different dimensions of impulsivity and Costa., *et al.* [46] who showed impulsivity in healthy males related to striatal dopamine transporter availability. Cao., *et al.* [47] using diffusion magnetic resonance imaging and probabilistic tractography method to examine whole-brain white matter (WM) in ADHD subjects showed decreased structural connectivity in the prefrontal-dominant circuitry correlated with the "inattention", but increased connectivity in the orbitofrontal-striatal circuitry, with the "hyperactivity/impulsivity" symptoms.

Subtypes differences in the treatment response

As early as 1970's, there have been reports of the link between the prediction of response to stimulants and hyperactivity/impulsivity and not the inattentive subtype. Loney., *et al.* [48] in 1978 reported the improvement of 84 boys aged 6 - 12 with the hyperkinetic/MBD syndrome to the treatment with methylphenidate, was related to their level of hyperactivity. Kimbal [49] in 1986 tested 17 children previously judged to be good or poor responders to methylphenidate on sensory integrative measures while in the off-drug state. Results showed that children who were poor responders to Ritalin showed prolonged scores on and an adverse reaction to the Southern California Postrotary Nystagmus Test and had poorer equilibrium reactions and lower double tactile stimuli scores than the children judged to be good responders to Ritalin. The author postulated "there are at least two discernible types of hyperactivity associated with attention deficit disorders (ADD) that are theoretically related to differences in vestibular processing: one related to under aroused or overinhibited lower brain centers, and another related to deficient inhibition from higher brain centers. The good responders to Ritalin appear to be the under aroused group, the same population that responds to sensory integrative occupational therapy techniques.

Aman and Turbott in 1991 [50] reported that none of the cognitive or attentional, but psychomotor performance tests predicted response to methylphenidate on 26 children with ADHD. Handen., *et al.* [51] in 1994 reported that impulsivity and activity level at baseline rated both by parents and teachers were associated with greater gains in response to treatment. Buitelaar., *et al.* [52] reported high IQ and young age as the predictor of response to methylphenidate. As it was mentioned earlier and I have discussed elsewhere [53], ADHD of hyperactive-impulsive subtype is associated with high intelligence. Also, since dopamine, the target of stimulants is influential in the brain development, or in a better word acts like a brain fertilizer, the younger the age the better response to stimulants [4]. This is contrary to the current pharmacotherapy practice in the treatment of ADHD, i.e. increasing the dose of stimulants like other medications, per increase of age, while in fact the dose of stimulants should be lowered as the patient ages. The determination of this young age, or age of the brain has been shown in the brain developmental studies [54] that the brain development still continues through the increase in the volume of gray matter in the frontal, parietal and temporal lobes through adolescence and increase in the brain foldings until mid 20's. This means that after mid-20's the stimulants may not be as effective as they are in children and adolescence and one may expect more side-effects. This fact has been recently summarized well in a meta-analysis of 44 studies involving 9952 adults treated with stimulants by Cunill., *et al.* [55] who reported, "Pharmacological treatment provides mild symptom improvement but is associated with frequent AEs and higher treatment discontinuation than placebo".

Later on to this date several more studies have confirmed the prediction of positive response to stimulants with hyperactivity, comorbidities with conduct or other externalizing disorders that are seen in ADHD-HI, and negative response with lack of hyperactivity and comorbidity with internalizing disorders that are observed in ADHD-I or ADD [56-58]. Kereszturi., *et al.* [59] like Eisenberg., *et al.* [40] have also showed that Catechol-O-methyltransferase (COMT) Val158Met polymorphism that is more abundant in ADHD-HI is associated with methylphenidate response. Recently there have been several trials of identifying neuropsychological predictors of response to psychostimulants. Coghill., *et al.* [60] and others have been able to identify high performance on the 'go/no go' task type 1 and poor performance

on Delayed Matching to Sample (DMtS) task as positive predictors and not any other neuropsychological measures including working memory tasks. The 'go/no go' task involves presenting the subjects with a sequence of letters and numbers on a screen, where the 'Type 1' block involves "switching attention" while the 'Type 2' block does not require shifting attention. Delayed Matching to Sample (DMtS) is a test of the ability to remember the visual features of a complex, abstract, target stimulus and to select from a choice of four patterns after a variable delay. This is compatible with the so far results of a self-report survey among ADHD subjects in a primary care community, that ADHD-HI while having difficulty in "sustain attention", they perform well in tasks requiring "switching attention", "divided attention" and have "selective attention", all needed for multi-tasking that these subjects outperform even normal controls [24].

Here I need to elaborate more on the selective, divided and switching attentions that I have labeled them elsewhere as "dynamic attentions" [4,61]. In selective attention, the subject needs the capability of selectively filtering out the non-interested objects, in a competition among multiple stimuli by a top-down attentional control. In alternating or shifting attention, there is a cognitive flexibility or the ability to change or shift attention between objects, fed by dopamine through deactivation of the medial Prefrontal cortex (PFC) and the posterior cingulate and activation of the lateral PFC, posterior parietal areas, and the striatum [62]. Hanania and Smith [63] assert that both selective and alternating/switching attentions require high intelligence and are developmental, starting in preschool years. Divided attention that is more and more a necessity of modern digital and fast paced life and is developmental, requires high intelligence. All these types of advanced attentions that are superior to so-called "normal sustained attention" demand the activation of a vast area of brain especially higher cortex. For example, selective attention activates globus pallidus, caudate nucleus, lateral orbitofrontal cortex, posterior thalamus/colliculus, and insular-premotor regions, while the divided attention activates the anterior cingulate and dorsolateral prefrontal cortex [64]. Solís-Ortiz., *et al.* [65] have also shown subjects with COMT Val/Val allele enzyme in prefrontal cortex has fewer errors in a selective attention task and were superior to those with Met allele in executive processes and cognitive flexibility.

Lastly Levy [66,67] has emphasized that the better lower psychostimulant dose response in children with ADHD corresponds to an "inverted u-shaped dopamine curve". This also supports the notion that ADHD individuals with the homozygous COMT (valine/valine) genotype who show better improvement with stimulants, have lower tonic, but higher phasic dopamine (DA) that is associated with hyperactivity and impulsivity, than working memory deficiencies, and more synaptic plasticity. Erixon-Lindroth., *et al.* [68] have also shown that there is a relationship of age-related losses of striatal dopamine transporter (DAT) density to age-related deficits in episodic memory and executive functioning. Most importantly, the age-related cognitive deficits were mediated by reductions in DAT binding, whereas DAT binding added systematic cognitive variance after controlling for age. Krause., *et al.* [69] have also showed no increase in DAT density in a group of adults with ADHD, in contrast with children with ADHD who at least some have higher DAT availability. This has a clinical significance in the treatment of ADHD across life span that means the dose of stimulants need to lower as the age increases, as in the adult age the density of DAT to transport the increased dopamine caused by the stimulants decreases by age. Lack of attention to this fact would lead to more side-effects with stimulants in the adults as mentioned earlier [56].

Also, the increase in the val allele of COMT across life span is consistent with the brain development, meaning that ADHD-HI is a developing brain condition than a neurodevelopmental disorder that could be the case with the inattention subtype or ADD [4,70]. The dopamine transporter DRD4 gene, specifically the variant "7-repeat allele" has also been strongly associated with cADHD (childhood onset ADHD) that persists to adulthood, opposed to other gene variants of DAT1 9 and 10 repeat alleles that have been associated with poor response to stimulants and perhaps mostly associated with the inattention subtype. This fact is also in contrary to the recent suggestions by some researchers that ADHD could have an onset even in adulthood and the adult ADHD may not be a continuum of childhood onset ADHD [69-71].

Conclusion

In summary and in resolution of ADHD homogeneity or heterogeneity, the current ADHD with its diagnostic criteria and subtypes in DSM5 seems not to be homogenous but heterogeneous with two distinct and unrelated subtypes of "inattention" and "hyperactivity/impulsivity". As it was detailed in this review paper, there are distinct slow attentional and cognitive process, speed and performance on the intelligence test of WISC-II in predominantly inattentive subtype (or ADD) than ADHD-HI subtype [10,12,14]. The heterogeneity of ADHD and the distinction between the two subtypes at a face clinical and symptomatic level and value and more so at an underlying pathophysiological level and value, as it has been explored in this review paper, has been already challenged and proposed by others [10,14,16], though this article has critically reviewed and summarized them all here with a clear conclusion as follow.

Therefore, it seems that the true ADHD is only the "hyperactive/impulsive" type and there is no evidence base for the existence of "inattentive" subtype of ADHD as a distinct disorder, related to ADHD. As a result, the combined subtype (ADHD-C) is not justified as it mixes the two distinct subtypes that have different symptomatic and pathophysiologic presentations, just for the commonality of "inattentive" symptoms cluster. This has stalled the ADHD research to reach more conclusive results, as it has combined two distinct disorders with two different pathophysiology under the same rubric. Based on some research that have differentiated and suggested heterogeneity of ADHD [10,14,16], I argue that the inattentive subtype (ADHD-I or ADD) could be a neurodevelopmental condition like autistic spectrum and learning disorders, while hyperactive-impulsive subtype (ADHD-HI) is the true ADHD and not a neuro-developmental disorder but a developing brain condition [6,19-22].

Our group has found that in contrast with the inattentive subtype (ADHD-I or ADD), ADHD-HI is associated with dynamic attentions of selective, divided and switching, while similar to ADHD-I (ADD) they may struggle with sustain attention (a research in the process of completion and publication). This attentional difference that has not yet been differentiated, explored and researched in the ADHD literature has been recognized as significant attentional components in brain development and intelligence [26-28,63-67]. The more dynamic and intelligent brains of ADHD-HI utilize more dopamine have been shown to possess higher DAT (Dopamine Transporter) in the subcortical and higher COMT (Cathecol-O-Methyl Transferase) in the prefrontal regions of the brain by carrying the genotype val-val allele of COMT [40,43-45].

In other words, ADHD-HI could be not due to "dopamine deficiency" [72], the dominant ADHD theory since the advent of stimulants by chance, but a result of "dopamine insufficiency" [4]. This new theory is compatible with the evidence of high density of DAT and COMT in the subcortical and prefrontal cortical areas of the brain in ADHD-HI, demanding higher levels of dopamine for the development and functions of such "hyperactive" or "hyperattentive" brains [26]. This concept is also in accordance with the evidence of highly dynamic attentions (selective, divided and switching) of these subjects who are capable of multi-tasking but having difficulty in sustain attention to the "non-interested" or "boring" tasks, not in the realm of their selective and fast paced attentions, such that is common in the classrooms [4,24,63-67]. The official separation of the current subtypes of ADHD will revolutionize not only the research field of this condition, but the whole psychiatry as it will move beyond symptoms counting and descriptive diagnosis. ADHD is the most heritable condition in psychiatry with > 75% concordance among identical twins and highly familial specially the hyperactive-impulsive subtype [73,74] that is the best candidate for genetic and pathophysiological studies if we only could overcome and change our current descriptive diagnostic system at least starting with ADHD.

Study Limitations

This paper has been based on a selective review of the literature on ADHD with focus on studies that have differentiated between the current subtypes of this disorder, phenomenologically and Pathophysiologically. Although the number of such studies are limited in the research arena, the difference between the two current subtypes of ADHD is so distinct that calls for more such research and differentiation of the subtypes and recognition of ADHD-HI as the real ADHD.

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