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3

Obsessive-Compulsive Disorders or Not: Differential Diagnosis of Repetitive Behaviors Among Individuals with Intellectual and Developmental Disorders

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1. Introduction

This chapter focuses on the complex psychobiology of Obsessive-Compulsive Disorder (OCD) among individuals with Intellectual and Developmental Disabilities (IDD). It begins with OCD as an anxiety-driven psychiatric disorder characterized by intrusive thoughts and images (obsessions) and a tendency to engage in a select group of escape behaviors (compulsions) of sufficient severity to interfere with daily life. Using these criteria to diagnose OCD in persons with IDD frequently results in a heterogeneous disorder that overlaps other forms as repetitive behaviors (Baldwin et al 2008; Pallanti et al 2008). Resolving the heterogeneity issue requires that we differentiate OCD from related stereotypies, ritualistic behaviors, self-injurious behaviors (Flavell, 1982), and OC-related behaviors associated with Autistic Spectrum Disorders(ASD),Tourette's Disorder (TD) and other movement disorders (Barnhill, 2008). To accomplish this task we will move beyond the descriptive criteria for OCD and anxiety disorders found in the Diagnostic and Statistical Manual- IV-TR (APA, 2000) and the Diagnostic Manual-Intellectual Disability (Fletcher et al, 2007). By the end of this review it will be readily apparent to the reader that OCD like other anxiety disorders represents a convergence of many functional abnormalities spread out across several neuro-anatomically distinct but functionally overlapping pathways. To reach this conclusion, we will come to understand that the symptomatic diversity of this group of disorders of repetitive thoughts and behaviors depends in large part on regional malfunctioning within a pathway or network rather than on any single "lesion" (Davis, 2002, Barnhill, 2008).

We will begin this exploration by examining fear, fear conditioning and their role in anxiety disorders. To do this requires an analysis of new findings in the neurosciences, especially gene-environmental interactions, temperament, physiological responses to stressful environmental events and the mode of anxiety-related behavioral responses (Feinstein et al 2007; De Mathis et al 2006) . Later, we will shift to an ethological model that uses reciprocal social, ritualized and attachment behaviours to describe subtypes of anxiety. This approach can be a useful tool can be useful tool for classifying OC related behaviors among nonverbal patients with severe- profound IDD. The remainder of the chapter will address the relationship between OCD, Obsessive-Compulsive Spectrum Disorder (OCSD) and

repetitive behaviors in other neurodevelopmental disorders -including intellectual disability (IDD) (Parsons et al, 1985; Ruedrich et al 1985; Pallanti et al, 2008) .

2. Neurobiology of fear and anxiety

Fear is a state of cognitive, emotional and physiological arousal that is triggered by the presence of a direct threat or danger (Costello et al, 2005; Mobbs et al, 2008). Fear responses are characterized by increased arousal and vigilance, increased sympathetic output, changes in perception and cognitive appraisal of events, and flight-fight responses (Britton et al, 2010). The cognitive-emotional components of the fear response result from increased autonomic activation (sympathetic nervous system), neuro-endocrine changes represented by an increased CRF and hypothalamic-pituitary adrenal activity (Charney et al, 2002)) and activity in the peri-aqueductal gray region involved in motor activity and pain perception (Mobbs et al, 2007). These physiological reactions generate flight, fight or freezing responses may vary depending on the imminence of the danger, context (ecological factors), proximity of the threat, presence of others, availability of behavioral responses (including defensive aggression), age and temperamental variability in the threshold and intensity of approach/avoidance behaviors. Several of these variables also play a key role of vulnerability factors for anxiety and anxiety disorders (Davis 1997, Stein et al 2002, Neumeister et al 2003). Freezing responses are not included in this review. But we cannot overlook this physiological response among pre-adults, especially as it relates to catatonic and dissociative behaviours among adults under extreme duress. (Harris et al, 1997; Stein et al, 2002; Lee, 2007; Britton et al, 2010).

Fear conditioning is a form of associative conditioning in which the state of arousal is linked to an external threat. Under these conditions, this physiological state is associated activation of the amygdala and related hypothalamic /sympathetic circuitry serves as the unconditioned stimulus. (Mobbs et la 2007; Stahl et al 2008). Activation of this system leads to increases in autonomic and neuro-endocrine activity that results in an automatic or unconditioned response that consists of flight-fight and freezing behaviors (Zohar et al, 1991). Current research also points to the amygdala as a critical component of in fear conditioning (Mobbs et al, 2007). Fear conditioning is due to a pairing of an unconditioned stimulus (an approaching hungry tiger) and conditioned stimuli (setting or specific environmental cues) and an unconditioned response (intense fear and flight or fight activation). In time, some specific features of the encounter or its environmental context can activate the fear responses and associated avoidance or escape behaviors. Fear conditioned experiences are also subject to generalization so that additional neutral or previously nonthreatening stimuli (secondary conditioned stimuli), such as returning to similar conditions or experiencing less intense affective states of arousal, can now trigger the cascade of avoidance behaviors. With repeated exposure and avoidance the behaviors may occur without clearly re-experiencing of the originating stimuli or context. These stimulus-response trains can expand to include more generalized avoidance behaviours. These permit the individual to not only escape, but also evoke protective responses from significant others. At this point, operant or response conditioning also comes into play.By eliciting family or peer support, this social contact can also reinforce avoidance behaviours (Sturmey et al 2002, Joy et la, 2003, Britton et al 2010).

Although operant conditioning plays a key role in maintaining avoidance or protection seeking, generalization usually involves a blending of reinforcement types. The conditioning experiences also reflect reconfiguring long term potentiation (LTM) and changes in neuronal-synaptic interconnections and communication (Hades, 1985). Repeated exposure can solidify learned associations by a process of sensitization that can eventually contribute to the automazation of these stimulus response chains into pre-potent responses. This consolidation of these conditioned event-response chains is the result of reconfiguring synaptic and dendritic connections that facilitate the recruitment of additional resources from other neuronal systems. This process serves as the foundation for generalization of fear-response chains and underlies the transformation to more generalized responses to vague or diffuse threats. This process is much like kindling in epilepsy, mood disorders and substance abuse. The end result of these transformations is increased resistance to extinction (Post, 2007; Hefner, 2008; Gorman et al, 2010).

In contrast to fear, anxiety is a state-related affective change that remains disproportionate to the reality of internal or external threats (Neumiester et al 2003). Anxiety-mediated behaviors represent the metamorphosis of a fear/flight-fight or freeze responses. In this respect, anxiety is the neurobiological analog to widely generalized fear conditioning that is now recruiting from a much wider neuronal field (Heilman, 1997). In time this field includes linkages between the extended amygdala, hippocampus, and brainstem nuclei for multiple neurotransmitter systems, hypothalamic connections including the sympathetic adrenal-medullary and hypothalamic-adrenal axes (Stahl et al 2008), insular, orbitofrontal, striatal, medial prefrontal, cingulate and other associational or heteromodal cortices (Cherney et al 2002; Kada et al 2003; Fudge et al 2003; Millhelm et al 2005). The complexity of these interactions suggests that although related to fear, anxiety involves higher levels of integration between nominally compartmentalized networks devoted to perception, more nuanced forms of affective expression, cognitions and motor responses (Davis 2002). Anxiety is experienced through extensive recruitment and cross-communication between these systems. To achieve this level of integration requires extensive interaction between prefrontal and associational cortices; highly processed sensory input; limbic and motor circuits; and complex memory functions (Northoff et al 2002; Britton et al 2010).

Recent data suggests that obsessions and compulsive behaviors are the result of dysfunctional gating mechanisms- dysregulation of limbic input.Recruitment of other cognitive and memory sources and compromised top down regulation from the hippocampus, prefrontal and other heteromodal cortices (Harmon-Jones et al, 2007). This imbalance permits threat and conflict mediated sensory input intrude upon ongoing cognitive activity and release an automatic, but restricted group of stereotyped behavioral responses. These compulsions temporarily reduce the need to respond to the perceived threat but often at the expense of more adaptive behavioral responses. As we shall discuss later, the ethological model suggests that some forms of OCD may arise from the release of selected ritualistic behavior as a means of resolving similar conflict-mediated responses. In either case these escape or ritualized responses are enhanced by operant factors, especially negative reinforcement (Sturmey et al 2002). These conditioned links are also subject to sensitization and evolving resistance to reversal learning and extinction (Post et al 1998).

Yet even though these learning experiences are universal, most people do not develop PTSD (Stein et al 2002; King 12010), panic disorder-agoraphobia (Stein et al 2008; Koh et al 2010), generalized anxiety (Schienle, 2011; Turk et al 2011) or OCD (Atamura et al 2007; Stein 2008)

or OCD. Later in this chapter we will address the underlying neurobiology of individual vulnerability to anxiety disorders but for now we will shift our attention to a group with significant deficits in adaptive and problem solving skills (fluid intelligence) as well as top down regulation of conditioned limbic subcortical responses.(Northoff, 2002; Stevens et al ,2007). This group includes individuals with IDD and autism (ASD). Individuals with severe IDD/ASD are also constrained by reductions in communication and problem solving skills as well as co-occurring brain disorders such as CP and epilepsy (Barnhill, 2000; Harris et al, 2009). These ADD: neurodevelopmental deficits also impact early attachment as well as interpersonal and emotional development (Althoff et al 2010). In addition, challenging experiences such as maternal depression, marital and/or family dysfunction, and extra-familial, psychosocial stress can overwhelm the individual's adaptive and problem solving skill (Hiem et al 2002;Haley et al 2003; Feldman et al, 2009) . Chronic stress can derail the neuro-endocrine regulatory organization and expression of stress responses while also adversely affecting new learning and more effective coping skills (Rueda et al 2007; Gunnar et al 2007).

Anxiety disorders are mental disorders characterized by negative affective experiences; specific patterns of responding to these state related changes; persistence; waxing and waning course and sufficient intensity to interfere with daily functioning (Costello et al 2005). Panic disorder (Nedstadt et al 2010) and OCD (Cooper et al 2007) appears more highly heritable than PTSD (Perez-Edgar et al 2005) or generalized anxiety disorders (Schienle et al 2011). Other anxiety disorders represent a more complex interaction between temperamental factors such as behavioral inhibition or high levels of neuroticism and life experiences (Merikanaga et al , 2009)). For these temperament-life experience dominated forms of anxiety, the major contributing factors may be less obviously genetic in origin and more the result of ongoing transactions between affective reactivity, negative emotional reactions to many environmental and social interactions; patterns of avoidance behaviors and life experiences. Another key factor is related to their high rates of comorbidity with other mental disorders (Perez-Edgar, 2005; Kagan et al 2007). But this is by no means a rigid asymmetry in gene-environment interactions. For example, until recently PTSD and other severe stress mediated conditions were considered as reactive disorders that occurred in response to overwhelming stress of aberrant social/emotional nurturing (Hiem et al 2002). Reality is not so simple. As we shall see later genetic factors associated with serotonin transporter protein activity (Sugden et al 2010), epigenetic changes affecting corticotrophin releasing factor receptors production and sensitivity and threshold of sympathetic arousal all play key roles in individual vulnerability to these stress reactions (Gunnar et al, 2007; Stahl et la 2008). These same forces are also operating in persons with IDD and ASD in which compromised adaptive and problem solving skills contribute to increased vulnerability and the high prevalence rates for anxiety related mental disorders in this population (Witwater et al 2008; Lunsky et al 2009).

3. Neuro-ethology and anxiety, anxiety disorders

Ethological analyses are useful tools for exploring the social-behavioural underpinnings of anxiety disorders. Their value is due in large part to the integration of neurobiology and social behaviour. This union provides into problems of social communication, reciprocity in interpersonal relationships and species-specific patterns of responding to perceived conflict. In this brief section we will apply ethological principles to subdividing anxiety based on its

relationship to threat and threat perception, patterns of ritualized behaviors during conflicted social encounters with social dominance, disapproval, territoriality and group synchrony. Included also are attachment and attachment-proximity-seeking behaviors (Harris, 1996; Barnhill, 2000b). This approach is of limited utility for understanding panic attacks per se but may be useful in analyzing separation anxiety (attachment)), patterns of avoidance and co-morbidity of OCD and Panic disorder. The following demonstrate a few of these ethological concepts:

3.1 Panic-defensive aggression

Panic disorder, PTSD phobias and social anxiety disorders display a pattern of exaggerated fear response, increased hypothalamic-pituitary-adrenal drive and activation of the sympathetic nervous system in response to selected stimuli (Charney et al 2002). Aside from some rituals seen among individuals with performance anxiety, most affected individuals try to escape or submerge their anxiety (Neurmeister et al 2002). Fear conditioning is a major factor in PTSD and panic disorders and escape or avoidance behaviors that can perpetuate symptoms (Stein, 2002; Cooper et al 2007). Panic and phobic responses are less likely to be associated with rituals but do appear analogous to some flight behaviors (Barnhill 2000a, b). As a result, some forms of defensive aggression may occur during panic attacks (escape routes blocked) or during a flashback or other intrusive experiences in PTSD. In addition less intense forms of defensive aggressive may function as ritualized displacement behaviors (Harris 1996; Barnhill, 2000b). Agoraphobia can lead to chronic social isolation and anticipatory and context-dependent anxiety about the occurrence of rare panic attacks. A curious aspect of agoraphobia involves an individual's ability to use key people to compensate for avoidance behaviors (Gorman et al 2002; Chavira et al 2005). In this circumstance, ritualized proximity seeking (attachment behaviors) can mobilize group "protective behaviors", but over time may reinforce avoidance behaviors.

3.2 Social anxiety, dominance hierarchies and appeasement gestures

Generalized social anxiety represents a pattern of avoidance behaviors in response to social exposure and fears of being humiliated (Chavira et al, 2005). Many of these behaviors are analogous to problems associated with dominance conflicts and defeat-related (Swedo, 1989; Harris, 1996; Barnhill, 2000). In this paradigm, social anxiety represents an over activation of threat perception (disapproval, ostracism or attack) coupled with a lower threshold for behavioral inhibition (temperamental trait); reduced habituation to repeated exposure and resistance to extinction. There is an interplay between behavioural inhibition and over-reactive adrenergic responses to perceived threat or disapproval. Both temperamental and neurophysiological responses are related to misinterpreting neutral or ambiguous facial expressions (Alfano et la 2009). These state and trait patterns of affective response may explain the extensive comorbidity of social anxiety with several other internalizing disorders (mood, social anxiety and some forms of separation anxiety) and OCD. In addition, among nonhuman primates defeat contributes to submissive postures and increased grooming dominant members of the group. These behaviours also have analogues in social anxiety disorder and OCD (Feinstein et al, 2007; Baldwin et al, 2008). For example, cleaning/grooming may have its origins in conflicts over social dominance that predate our modern pre-occupation with germs. Ritual impurity or failing to live up to social group norms most likely predates contamination/cleaning rituals and checking rituals (Seuss et al 1989; Zohar et al 1991). OC Spectrum disorders like BDD and other disorders of excessive

grooming may have similar origins. The need to escape such situations may play a more significant role in OCD than in the approach-mediated behaviors associated with some OCSDs.

3.3 Attachment- proximity seeking

Disrupted attachment and exaggerated proximity seeking behaviors create long term risks for psychopathology. Genetic risk factors for mood/anxiety disorders influence the transition from compromised attachment to psychiatric disorders (Koda et al, 2003; Barnhill 2007a; Ursano et al 2007). Lacking this genetic vulnerability, children with ambivalent and disorganized patterns of attachment remain at risk for both internalizing and externalizing disorders. Current social neuroscience research suggests that ongoing parental non-responsiveness, asynchronous reactions to infant signals, as well as abuse and neglect influence gene activation and modulation of stress response pathways (Gunnar et al 2007). These epigenetic events are critical to shaping the organization, intensity and threshold for neuroendocrine and sympathetic nervous system responses to later separation (Koda et al 2009). In the long term, these events result in an increased risk for deficits in stress and anxiety tolerance (Reiss, 2002), exploratory behaviors (Matthews et la 2008), threat perception and mastery of demands and new learning (Gunnar et al, 2007) . They can also influence exploratory behaviors, novelty seeking and involvement in key social learning experiences. Exaggerated sensitivity to danger or threat cues from parents and proximity-seeking attachment behaviors can be shaped by operant farces (social reinforcement). . These events influence the development of reactive attachment disorder (Barnhill 2007b), separation anxiety (Suveg et al 2005; Stahl et al 2010) , panic disorder/agoraphobia and later developing personality disorders (Hiem et al 2003; Feldman, 2009; Posnin et al, 2009; Knapp et al, 2011).

3.4 Rituals- compulsions

Ritualization in ethological terms represents a pattern of repetitive species-specific behaviors that can defuse ambiguous social confrontations, decrease the likelihood of attack, and convey social information about dominance (Harris 1996; Barnhill 2000 a and b). Ritualization in this sense lies on a continuum between obsessive and selected repetitive behaviours. As we shall see, transient rituals occur during normal development (Leonard, 1989). Dysfunctional rituals are more likely to occur in individuals with anomalous brain development (prefrontal injuries and perseveration); territorial and dominance challenges (social space and status issues); genetic risks for OCD; ASD and severe IDD (Pauls et al 2002; Bucan et al 2008); and degenerative disorders affecting fronto-striatal regulatory pathways (Mataix et al 2008). These behaviors are analogous to fixed action patterns (ritualized display behaviors) triggered by innate releasing mechanisms (social threat and conflict) (Swedo 1989, Harris 1996, Barnhill 2000b). Problems with excessive grooming behaviours are also driven by working memory deficits, difficulty disengaging from ongoing behaviors (checking behaviors) and worries about violating social taboos or cultural norms. These neuropsychological deficits play a role in contamination and cleaning rituals- especially in societies lacking our concerns with sanitation and cleanliness (Seuss et al 1989). This ethological/social acceptability subgroup also provides insights into BDD, anorexia nervosa, hypochondriasis and trichotillomania (Barnhill 2007; Fineberg et al 2006).

An ethological focus is of greatest value for clinicians dealing with nonverbal persons with severe-profound IDD. It is quite helpful to have a good working knowledge of ethology as a means of understanding nonverbal communication as it relates to aggression, SIB or stereotypies (Flavell, 1982). An ethological focus can also be useful in integrating information about challenging behaviors drawn from functional behavioral analyses-especially behaviors that appear mediated by social attention, or as a means of communicating pain or distress (Hall et al, 1992; Petty et al 2009). Self-injurious behaviors evolve during childhood from nonverbal forms of proto-imperative communication of immediate needs. In vulnerable children, these "distress" behaviors can morph over time from escape or avoidance behaviors into severe SIB. This transformation suggests roles for both associatively conditioned automatic responses and those operant learning experiences that serve to maintain by negative reinforcement. The missing piece is what forces shape this transformation in some individuals and not others (Flavell et al, 1982; Hall et al 1992; Hall et al 2001; Gardner , 2002; , Oliver et al 2005).

An ethological model also segues into integrating social responsiveness and communication, generalization of earlier learning experiences and sensitization/interactive specialization (changes in the molecular dynamics of gene, neuronal, and neurotransmitter adaptations). Ethological data can also provide a useful starting point for defining endophenotypes of ritualistic/anxiety mediated behaviors among individual with OCD, ASD, and SPID.

4. Developmental sources of anxiety and repetitive behaviors

Repetitive behaviors are common throughout much of childhood. Developmentally appropriate magical thinking and rituals help young children cope with normal childhood fears and anxieties. Later in childhood these rituals are incorporated into games, or "harmless habits" or superstitions (rabbit's feet, whistling past graveyards, salt over the shoulder). By late latency hero myths and fairy tales permit unconscious reworking of earlier anxieties. They allow the child to join the hero as he or she masters new concerns about family, academic performance in industrialized societies, and learning gender specific social roles, adult occupational skills and the intricacies of ritual life in non-industrialized settings (Leonard, 1989; Vaccarino et al, 2003; Barnhill, 2008b).

Later in childhood, rapidly developing cognitive-reasoning skills and approaching puberty signal another transformation. The ascendency of concrete and later formal operational thought permit future planning and worries, growing independence from the family of origin and emergence of issues related to status In the social hierarchy. By late childhood and early adolescence peer disapproval replaces perceptions of parental disapproval as a source of social anxiety (Gunnar et al 2007). In addition, cognitive maturation further insulates the child from the re-experiencing these childhood fears and magical thinking by binding them to more complex cognitions and defense mechanisms. In industrialized societies, these cognitive changes set the stage for an increasing reliance on scientific-rational causality. As a result magic devolves into entertainment as scientific modes of thought replace supernatural causality. Discordant or idiosyncratic religious beliefs can also foster anxieties about meeting the demands of religious communities. Among persons vulnerable to OCD these uncertainties are transformed into pre-occupations and ruminations (Suess et al 1989; Leonard et al, 2005; Barnhill, 2008).

Collective forms of fantasy and imagination are represented in magic and supernatural beliefs about causality (Seuss et al, 1989). For older children make-believe is replaced by shared social rituals and some devaluation of earlier modes of coping with of childhood fears. Yet even though reality is distinguished from earlier modes of thought and emotional expressiveness, these boundaries remain semi-permeable. During periods of stress or in creative play the boundary between ritual and realization is crossed by superstitions such the odd dressing and on field behaviors of some athletes, attempts to avoid stepping on cracks in the side walk, knocking on wood etc (Ursano et al, 2009).

During late childhood, and on into adolescence there is a growing divergence between adaptive fantasy and rituals of neuro-typical and those found in persons with IDD. For children with IDD, these earlier modes of fantasy-ritual expression may continue, leaving clinicians in limbo regarding whether these residual expressions are the result of developmental delays or "fixations" relative to developmental age- e.g. playing with toys or building blocks after coming home from high school or watching the same cartoon as a younger sibling (Leonard 1989). Children with ASD on the other hand, may have limited interest in play or social fantasy and prefer instead to line up toys or "play" alone. In a similar vein children who are genetically at risk for OCD are already expressing worries and rituals of at risk children differ from those of "normal children" (Black et al 2008; Baldwin et al 2008). For vulnerable children, magical beliefs, superstitions and rituals do not resolve but morph into patterns that are consistent with sub-clinical or full syndrome OCD. Not all children who reach this sub-clinical stage however will progress to full-blown OCD (Black et al 2008).

These changing patterns of magical beliefs, reasoning and ritualistic play do not occur in a vacuum but in the context of expanding social interests and desire to fit in. Successful transitions facilitate resilience in the face of complex endocrine andneurobiological changes. For example, social and learning experiences are shaped by temperamental factors (e.g. behavioural inhibition and high harm avoidance); deficits in language, social and cognitive skills; imaginative play and anxiety-mediated limits on exploratory behaviours and experiences with toys and enriching environments (Barnhill, 2008). By mid-adolescence there is a surge in the expression of genetic risk for specific disorders such as mood disorders, social anxiety and OCD. This is also a time when genetic vulnerability (positive family history), sexual maturation and yearning for novel experiences, an emerging developmental imbalance between heightened sensitivity to potential rewarding stimuli and need for external events to maintain positive affective states and maturation of top down regulation play increasingly critical roles in neuro-typically developing youth (McClure et al 2007; Kiddle et al, 2011).

This transformation overlaps the emergence of social anxiety, panic, OCD, major depressive disorder, OCSD/addictions in at risk children (Crews et al, 2007; Beesdo et a; 2009; Franc et al, 2010). These changes are also occurring among individuals with IDD and ASD (Joy et al 2003;. Cooray et al,2007). These some children with mild IDD face an additional problem- the growing realization that they are different and alienated from their peers. For adolescents with ASD/IDD uncertainty, limited ability to intuit social cues and impaired language pragmatics create increasing levels of stress and escalation in worries, and regression to modes of ritualistic behaviors (Barnhill, 2008; Jacob et al, 2009; Balemans et al 2010; Smith et al, 2010).

5. The problem of dimensional variability of OCD among individuals with IDD

OCD is an anxiety disorder characterized by intrusive thoughts and repetitive behaviors actions that interfere with a variety of daily activities and routines. Current data suggest that the prevalence rates for OCD range between 1 -2% of the population (Costello et al, 2005; King et al 2007;). The prevalence rates triple if we expand to include at risk individuals or those with subsyndromal OCD (failure to meet full criteria for OCD (Mataix e al 2008; Siminoff et al, 2008). Longitudinal studies also suggest that nearly 50% of this group will develop full syndrome OCD in time. Those converters are characterized by an early age of onset, positive family history of OCD and additional comorbid anxiety disorders (Murphy et al 2003; Black et al, 2008; Ginsberg et al 2008).

In behavioral terms OCD is a response to distress created by disturbing cognitions, images, urges (obsessions). These experiences trigger a restricted set of avoidance behaviors (cleaning, checking etc). These behaviors provide temporarily relief from the dysphoria and anxiety associated with obsessions these experiences. This pattern is best characterized as an escape from aversive cognitions (negative reinforcement). Over time these escape behaviors become increasingly ingrained and resistant to nonsystematic approaches to extinction (Noll et al, 2002; Prado et al, 2008; Sukhedalsky et al 2010).

Recent factor analytic studies report four major subgroups of obsessive and compulsive symptoms. These are pure obsessions, obsessions with compulsions such as anxiety about contamination leading to cleaning rituals; uncertainties about the completeness of actions contributing to doubting and checking; increased urge to arrange and order, organize and seeking balance in symmetry of thought and action; and hoarding (DeMathis et al , 2006; Mataix-Cols et al, 2008; Saxena, 2008). In addition to OCD, there are two subsets of OC-like symptoms, hoarding, and arranging, symmetry, counting and ordering rituals that are currently classified as Obsessive-compulsive Spectrum Disorder (OCSD). OCSD is further characterized by compliance with premonitory urges that differ from avoidance or escape from adverse emotional experiences or resulting behaviours (obsessions and compulsions). In addition, this group of patients also display higher rates of impulse control disorders and a propensity to react with anger or aggression when these repetitive behaviours are restricted(Fineberg et al 2007; Barnhill 2008; Pallanti et al, 2008). People with OCSD also differ from those with OCD in terms of high novelty seeking (impulsive risk taking) rather than behavioral inhibition/harm avoidance, and findings from neuropsychological testing, neuropharmacological trials and neuroimaging studies (Barnhill, 2008). These studies also note the relationship between intrusive aggressive, sexual or asocial urges and impulses and tic disorders. These studies also link hoarding with tic disorders and ASD (Kana et al 2007; Pallanti et al 2008, Saxena, 2008)).

Many individuals with IDD/ASD and severe sensory abnormalities also engage in stereotypic behaviors that function as an escape from overstimulation (Sayers et al, 2011). A similar pattern of escape-mediated, repetitive behaviors is also associated with psychophysiological distress secondary to pain, medical disorders, medication side effects and other environmental factors. In addition, individuals with IDD frequent display lower levels of stress tolerance, display exaggerated emotional, cognitive and behavioral reactions to environmental or interpersonal disruptions. Regressive behaviors in response to such stressors can also serve an escape function. Although not classified as OCD or OCSD these behaviors are likely to persist (negatively reinforced behavior), generalize and become increasingly resistant to extinction. It is noteworthy that the function and pattern of

reinforcement for these behaviors is similar to that seen in obsession-triggered compulsive behaviors observed in OCD. Typologically, they differ in terms of a more diverse repertoire of repetitive behaviors than associated with OCD (contamination/washing-cleaning and doubting checking). These subtle differences pose problems with the differential diagnosis of OCD in persons with SPID (Noll et al 2002; Hoch et al, 2002; Barnhill 2008; Petty et al, 2009) .

We can also expand the 4-factor model of OCD by including food seeking and hoarding; impulsive-compulsive behaviors associated with compulsive computer use, stealing, shopping; pre-occupation with and compulsive attempts to correct quasi-delusional beliefs about dysmorphic appearance or disturbed body image (body dysmorphic disorder and anorexia nervosa) (Barnhill, 2007); self-grooming behaviors (skin picking, trichotillomania) and hypersensitivity to body sensations and uncertainties about health (hypochondriasis) (deMathis et al 2006; Stewart et al, 2008). Many of these OCSD symptoms are accompanied by comorbid anxiety/mood disorders, unstable negative affective responses associated with personality disorders (Borderline Personality Disorder) (Niedstadt et al, 2011); impulse control disorders including ADHD (Rifkin et al 2007; Farrone et al, 2010), other disruptive behavior disorders and addictions(Stevens et al 2007; Barnhill, 2010), delusional disorders, psychosis and schizophrenia; fronto-temporal dementias and other neurodegenerative disorders (Barnhill, 2008).

6. Autism, obsessive-compulsive behavior, and intellectual and developmental disabilities

Autism is a neurodevelopmental syndrome characterized by behavioral deficits in social functioning, language acquisition and usage, overly restrictive cognitive and inflexible behaviors and interests (Joy et al, 2003; Novotny et al 2003). Once considered a rare disorder, current data suggest that the actual prevalence rates for autism and related disorders (ASD) may be as high as 1:150 to 160 children (Ronald et al 2001; Jacob et al, 2009). The most likely reasons for this surge in prevalence rates include: changes in diagnostic criteria that widen the net for children at the mild end of the spectrum; heightened awareness among parents, classroom teachers, primary care physicians and mental health professional; better diagnostic tools; recognition of milder forms of ASD (Welschew, 2007), especially those not associated with intellectual disability; and the increasing potential impact of environmental toxins (Gunnar, 2007; Johnson et al, 2007; Siminoff et al 2008). In recent years there is an increasing emphasis on earlier recognition and implementation of aggressive behavioral interventions. This drive is in part related to data supporting more dramatic improvements from highly focused and intensive treatments during toddlerhood. The long term goal is to alter the developmental trajectory of children with ASD and IDD (Myers, 2007; Schaer et al 2007; Howlin et al, 2008)

These prevalence studies also point out several features not addressed in the diagnostic criteria. One major finding is the strong gender dimorphism in which males are at least 4-5 times more likely to express ASD (Avramopoulus 2010; Grafodotskaya et al, 2010; El-Fishaway et al, 2011). This degree of dimorphism is most dramatic among male probands in families with more than one affected child (multiplex families); increased frequency of ASD among first degree relatives; and in families in which one or both parents express subsyndromal impairments in social communication and cognitive/behavioral inflexibility

(expanded behavioral phenotype) (Travis et al, 1998; Novotny et al 2003; Lunsky et la 2009). These findings dovetail into the ongoing genetic research that argues for the role of polygenic inheritance of rare alleles is responsible for heritability rates approaching 90% for ASD. But heritability studies run into a roadblock in singleton families in which only one child in the sibship is affected. ASD in these families is most likely linked to with known IDD, chromosomal and genetic/metabolic syndromes. Examples include conditions such a tuberous sclerosis, Rett's syndrome, phenylketonuria, Angelman's syndrome, FRAXA and nearly 40 other syndromes. Singleton families who chose not to have additional children can create similar uncertainties in the heritability data (Betancur et al, 2010; El-Fishaway et al 2010; Ronald et al 2011).

Neuroimaging studies of probands with ASD provide strong evidence for aberrant early brain development that includes neurogenesis, cell migration, white matter and structural organization of the brain regions such as the cerebral cortex, cerebellum and greater amygdala (Schaer et al 2000; Leckman et al 2003) . Microscopic analysis reveals problems with dendritic and synaptic integrity and stability, arborization and cellular maturation (Novotny et al, 2003). When combined, these findings reinforce the heterogeneity of ASD as well as support the final common pathway hypothesis (Betancur et al 2010) . Support for the idea of a final common pathway also comes from studies of primary and secondary ASD, and indirectly, from studies involving discordant monozygotic twins; and symptomatic diversity among multiple probands in multiplex families. From this data we can conclude that ASD is the result of multiple genes that influence and are influenced by complex gene-environmental and brain-behavior interactions (Ramocki et al 2009; Balemans et al, 2010; Ronald et al 2011)..

There are higher rate of comorbid psychiatric, neurocognitive (limited interests), language based learning disabilities and communication disorders (deficits in communication pragmatics and stereotyped speech) among families with ASD probands (Tavis et al, 1998; Smith et al 2010). The presence of OC-like symptoms lends further support the polygenic inheritance and the degree of overlap with OCD, Tic Disorders and ADHD (Barnhill, 2005). This data also reveals that the risk for ASD drops off rapidly when investigators focused on more distant relatives. These findings also suggest an answer to the clinical observation that many patients with treatment resistant OCD (Jacobs et al, 2009), and OC Personality Disorder (Baldwin et al, 2008) may in fact present with undiagnosed ASD. A downside to this argument is that when OCD and ASD co-occur, it is the ASD that exerts the more profound effects on both treatment response and clinical outcome. Both ASD and OCD are syndromes characterized by high heritability but different patterns of brain neurodevelopmental anomalies (Volpe, 2000; Joy et al, 2003; Knapp et al, 2009). With caution, there are differences can be useful for defining endophenotypes of OC behaviors and designing neuroscientific and neuropharmacological research (Hounie et al 2006; Jacob et al, 2009).

7. Behavioral phenotypes, ASD, OC behaviors

There are several behavioral phenotypes that are useful in teasing out and defining genetic subtypes of OCD among persons with IDD and ASD (Feinstein et al 2007; Levitas et al 2007). For example, Fragile X syndrome (FRAXA) is an X-linked form of IDD associated with a behavioral phenotype characterized by gaze aversion, speech dysfluency, social anxiety and

avoidance behaviors, repetitive behaviors and increased risk for complex partial seizures and paroxysmal episodes or panic-like symptoms. Males with the full syndrome are frequently diagnosed with ASD (Joy et al 2003; Lambroso et al 2008). On closer inspection, many affected individuals present with anxiety that appears more closely related to social anxiety and exaggerated avoidance behaviors than compromised social communication observed in ASD. Among both pre-mutational as well as full-syndrome females, there are increased problems with neurocognitive deficits, difficulties with social relatedness, and language development. In both groups, the preservation of social relationships in familiar settings become useful tools in the differentiating ASD from FRAXA without ASD (Barnhill 2000a and b).
Prader-Willi/Angleman's, Cornelia de Lange, Rett's (Ghidoni et al, 2007; Cahro et al, 2010), Velocardiofacial (Gothelf, 2007) and Chromosome Xq15.13 duplication are associated with ASD, OC related repetitive behaviors, IDD, and social communication deficits. A substantial minority of individuals with 15q11-13 duplications present with ASD based on impairments in cognition, social relatedness and behavior. Many affected individuals also present with increased rates of anxiety/OC spectrum disorders (El-Fishaway, et al 2010). For most, the typology of OC behaviors does not meet the criteria for OCD but instead present with hoarding, SIB, skin picking, aligning, arranging and other rituals (Levitas et al, 2007). Under these circumstances the diagnosis of OCD may not be appropriate and are best classified as Stereotypic Movement Disorder (Barnhill, 2006; Barnhill et, al 2007).

8. Obsessive-compulsive disorder, repetitive behaviors, and abnormal movements

The co-occurrence of repetitive behaviors, intellectual disability, and underlying movement disorders provides a viable test case for investigating a hypothesized linkage between repetitive behaviors, tics and abnormal movements, fronto-striatal dysfunction and psychopathology (Welschew et al, 2005; Barnhill, 2005a; Joostin et al, 2010). Aside from neurodegenerative syndromes, most movement disorders are characterized by waxing/waning and topographically variable patterns of repetitive movements. Most are also associated with cognitive, emotional and behavioral symptoms that are associated with dysfunctional fronto-striatal-limbic and ventral basal ganglia systems (Robertson et al, 1996; Barnhill, 2007b). In Tourette's Disorder, most affected children present with simple motor and vocal tics. But 5-10% may progress to more complicated movements. This group may also develop prodromal urges or sensations to move. Ticqueing can temporarily satisfy this state of heightened motivation. A feeling that things are "just right" frequently terminates these apparently voluntary motor actions. In addition these behaviors also permit the individual to escape from the unpleasant or annoying sensation (Leckman et al 2003; Prado et al 2008; de Mathis et al 2010). There is considerable overlap between neuronal circuits involved with these escape functions and negative reinforcement, OC behaviors and abnormal movements. Upon closer analysis however, the abnormal movements are neither voluntary nor involuntary but appear related to urges rather than anxiety. These responses represent a mixture of voluntary, repetitive motor responses to involuntary urges to think or act. Although this mixture of motivational states is also characteristic of OC spectrum disorders (OCSD) additional research is needed to differentiate these behaviors from complex sensory tics (Robertson et al 1996; Nedstadt et al 2010).
The onset of OCD in males under 5 is associated with the emergence of tics within three to five years of onset. These boys belong to families with loading for both Tourette's disorder

and OCD. Young girls share different ages of onset, clinical symptomatology and clinical outcomes. For affected females are genetically at risk and far are more likely to develop obsessive-compulsive disorder. This observation suggests a gender bias towards obsessive-compulsive symptoms rather than motor or phonic tics (Nedstadt et al 2010; Grados et al, 2010). There are also phenomenological differences between obsessive-compulsive symptoms associated with tics and those without. For example, contamination/cleaning and doubting/checking rituals are less common among individuals with tics (Rasmussen et al 2002). The group presenting with tic disorder is more likely to develop arranging, organizing, need for symmetry, and various impulsive-compulsive symptoms (Leckman et al, 2003). Even though obsessions are less likely, intrusive images or aggressive sexual or religious preoccupations are more likely (Suess et al 1989; Pallinta et al, 2008; Jacob etc al, 2009). Obsessions in tic disorders appear analogous to mental tics or perhaps intrusive symptoms observed in PTSD (King et al, 2010). As noted above, premonitory urges present as a building tension that frequently precedes complex tics among individuals with tic disorders (Leckman et al 2003; Prado et al, 2008). In general, attempts to inhibit these urges do not generate anxiety, but instead contributes to an increasing intensity. This contrasts with the usual anxiety/obsession-driven, ego alien behaviors commonly associated with OCD.

Among individualswith ASD these difference can be more difficult to appreciate (Barnhill, 2007b; King et al, 2007). These distinctions are even more difficult to make among individuals with co-occurring SPID. In this population it is difficult to differentiate these more ambiguous repetitive behaviours from complex tics and stereotypies/ritualistic behaviors. For example, self-injurious behavior is also associated with severe tic disorders with IDD/ASD (Barnhill, 2005a). In affected individuals SIB presents in at least three forms. One presents as the consequence of a low intensity/high frequency pattern of repetitive behaviors that eventually result in tissue damage. Cuticle and other forms of skin picking, nail biting and trichotillomania are examples (Leckman et al 2003; De Mathis et al, 2006) . These "aberrant grooming behaviors" frequently occur during "down time" or reduced environmental stimulation. Severe SIB on the other hand can occur in "binges" of high frequency/high intensity repetitious hitting, nail pulling, and eye poking, touching hot objects and other driven-behaviors. These usually terminate when the individuals reports that things now "feel right." Another group is triggered by prodromal sensations, pain and discomfort. Their SIB is directed at the affected body part. There appears to be some overlap between this form of SIB and Lesch-Nyhan syndrome (Levitas et al, 2007), neuro-acanthocytosis and other neurogenetic behavioral phenotypes (Barnhill, 2003; 2010). Two characteristics are especially striking: persistence of SIB in spite of intact pain perception and the frequent use of self-restraint to interrupt the compulsive drive to self-injury (Barnhill 2003a, 2005b; 2010).

The treatment of OC behaviors in individuals with Tourette's disorder also differs from commonly used treatment interventions for patients with OCD. For example, habit reversal therapies appear more effective for tic/OC behaviors than exposure-response prevention, and cognitive-behavioral training (Roblek et al 2005; Howlin et al, 2009). One explanation is that tic-related OC behaviors are less likely to have associated obsession or premonitory urges that signal the individual to initiate the program. A second but not exclusionary explanation involves differences in the underlying neurobiology of tics/OC behaviors- e.g. differences in pre-movement potentials, caudate activation and medial prefrontal activation that render repetitive behaviors as habits rather than anxiety-driven behaviors. These

differences may also explain why individuals with tic disorders and co-occurring obsessive-compulsive behaviors respond better to habit reversal than exposure-response prevention programs while being less sensitive to SSRIs to the point of frequently requiring a combination of SSRIs and neuroleptic drugs (Myers et al, 2007; Pallanti et al 2008; Stein 2008; Leckman et al 2003).

9. IDD, ASD and anxiety as developmental phenomena

IDD and ASD are the result of ongoing gene-environment interactions beginning during prenatal development. Many genetic disorders associated with IDD display considerable variability in terms of severity, dysmorphology, age of recognition and rapidity of psychomotor regression (Vacarrino et al, 2003; Barnhill, 2004; Bagot, et al 2010). The natural course of many of late-onset genetic disorders displays periods of autism-like behaviours. These transient "autisms" can be confusing to clinicians, especially for children with milder forms of the neuro-metabolic disorders. This pattern can also be seen in children with ASD but without IDD Bagot et al 2010, Betancur, 2010). Many parents of probands with ASD report that "something isn't right" with their infant. Unfortunately many describe a vague sense of emotional disengagement or disinterest in reciprocal parent-infant verbal and imitative "play". Other parents report "normal development" until 18-24 months of age followed by a regression in language about the time the child begins combining words into "sentences". A third group described dramatic regression to autistic like behaviors Beginning around 4 years of age, many of these children regress neurologically at highly individualized rates of decline. This subgroup is currently classified as Childhood Disintegrative Disorder (Novotny et al 2003).

Recent infant research describe early aberrant social interaction, lack of consistent response to their name and shared attention beginning between 9-18 months of age. In neuro-typical infants this period is associated with increasingly sophisticated reciprocal interaction, emergence of joint attention as both emotional engagement and early "learning" about the environment (Knap et al, 2009) . Social neuroscientists suggest that this emotional dance is involved in priming and entraining the language cortex (interactive specialization) (Fries et al 2007). In children at risk for ASD, this is also a time of a rapid expansion of head circumference and maturational disturbances in facial processing, emotional memory, and a preference for inanimate objects over human faces (Volpe, 2000, De Haan et al, 2009). Behaviorally these changes include emotional and social detachment, impaired locking onto speech and communication, emotional play, joint attention and pleasurable sharing with others (Knutson et al 2007; Dawson et al, 2009).

In general, the developmental impact of this impairment is related to the severity of ASD plus IDD. In contrast, infants with IDD only display attenuated but largely functional interests in social interaction, rudimentary communication and emotional attunement to parents (Fries et al 2007; Grey et al 2010). The presence of severe neurodevelopmental disorders also increases the probability of temperamental differences such as increased irritability, negative affective reactions to novelty or change, poor affect regulation and behavioral inhibition. During toddlerhood, behavioral inhibition is a risk factor for mood and anxiety disorders (including syndromal and subsyndromal OCD) later in life. Toddlers with high levels of motor activity, irritability, impulsivity and poor affect regulation are more at risk for high rates of repetitive behaviors and externalizing behaviors (Kagan et al,

2007). This group may be at greater risk for ADHD and in some cases disruptive behaviour disorders, addictions and some forms of OC spectrum disorders (Feinstein et al, 2007; Jacob et al, 2009).

This brief portrait of early development suggests a complex transaction between the infant, parent and the psychosocial environment. In addition to IDD and ASD, neglect and abuse can also have a profound effect on emotional attachment and sense of basic trust (Knapp et al, 2009). Maternal depression may also be equally distressing. The infant cannot elicit maternal responsiveness and will try valiantly to engage the affected parent. The chronic lack of intuitive nurturance and emotional responsiveness to the infant can result in the dysregulation of both the hypothalamic- pituitary- adrenal and sympathetic adrenal medullary pathways (Skuse et al 2003; Feldman et al 2009). At a behavioral level these changes compromise cognitive development and increase the risk of persistent high levels of emotional and neuroendocrine over responsiveness. Neurophysiological changes also impede novelty learning, exploratory behaviors and increase the levels of ritualistic and repetitive behaviors (Stahl et al, 2005; Romocki et al 2009; Joosten et al, 2010).

10. Genes, ASD, OCD, tic disorders and repetitive behaviors: A synthesis

For OCD, it is difficult to isolate a single gene, precise neuroanatomical lesion or single neurotransmitter system responsible for this syndrome (Murphy et al, 2003; Lehman et al, 2010). Functional neuro-imaging studies point to disequilibrium between the prefrontal-caudate, striatal and anterior cingulate prefrontal regulation (Pauls et al, 2002; Schaer et al 2007)). Neuropsychological studies point to problems with set shifting and regulation of sensory- motor responses, manipulation of social cues and decision-making. These findings support dysfunction in the fronto-striatal, limbic anterior cingulate, ventral striatum and multi-modal sensory cortices (Anderson et al, 2004; Mataix-Cols et al 2008)). Neuro-ethological studies describe regulatory deficits in terms of a"breakthrough" of grooming, territorial and conflict mediated ritualized behaviors (Harris, 1996; Barnhill, 2000b). Neuro-pharmacologically, there are both similarities and major differences between serotonin, dopamine, glutamate, opiate and other peptides and GABA systems. Many of these studies also reveal neurobiological differences between OCD and related OC behaviors (Pauls et al, 2002; Reinblatt et al, 2006; Waslick, 2006). These observationsmay explain the contributions made by overlapping but dysfunctional neurobiological mechanisms that underlie OCD and OCSD- the disruption in the convergence of social-emotional perceptual processing and the cross-talk between multiple neuronal networks involved in integrating and responding to this input. In this sense, OCD is but one possible expression of a dysfunctional pathway that can no longer efficiently reglate multiple interconnected systems of neurons.

The qualitative difference between the degree of impairment in social communication and cognitive/behavioural inflexibility are useful tools in the differential diagnosis of ASD from OCD among individuals with IDD (Barnhill, 2005a; Jacob et al, 2009; Ronald et al, 2011) . Persons with ASD but without IDD still display high levels of executive deficits, compromised coherence, language pragmatics and higher modes of social-emotional information processing. These differences also suggest fundamental differences in the timing of the "insults"- for ASD and IDD during embryological and early developmental; OCD somewhat later during maturation of regulatory pathways Barnhill, 2004; Northoff et al, 2006; Hofvander et al, 2009) For autism and schizophrenia the expression of these aberrant gene-environment interactions impact embryological events associated with neuro-genesis, cell migration,

differentiation/maturation and stabilization of dendritic pathways (Betancur, 2010; Gorman et al 2010). At the other end of the gene-environment dimension, PTSD was once considered to result from overwhelming external stress (Stahl, 2010; Sugden et al 2010; Qureshi et al, 2011). Genetic risk factors or gene-environmental interactions were considered to be bystanders. This assumption proved premature. It also appeared that the neurodevelopmental events associated with OCD, mood and anxiety disorders fell somewhere in between. Full expression of these disorders provides more room for epigenetic effects- the phenotype for many late onset mental disorders require a second or third "hit". For example, the second hit for OCD may be the presence of tic disorders/basal ganglia disorders, gender effects, and in some cases, an additional developmental or acquired insults for full expression include PANDAS (Asbhar et al, 2005; McNally et al 2008),traumatic brain injury (Vasa et al, 2004; Max et al, 2011); onset of depression and neurodegenerative disorders (Barnhill, 2008b).

Genetic studies thus far reveal more than 100 separate alleles of interest associated with ASD (El-Fishaway et al, 2011). Many involve promoter or regulatory genes, histone chromatin and gene activation/deactivation during critical periods of embryological and postnatal brain development; localized protein production; aberrancies in several key neurotransmitter and intracellular pathways and disruption of signals for neuronal differentiation, dendritic activity, pruning and myelination (Gorman et al, 2002; Bird et al, 2008; Lombroso et al 2008). Each of these gene- environment interactions impact brain-behavior interactions that underlie the core symptoms of ASD. Many also play key roles in learning/memory; challenging behaviors and behavioral phenotypes among individuals with IDD; temperament/emotional processing/affect regulation, language development, social reciprocity and mental disorders (Kana et al, 2007; Vicarrino et al, 2008).

Data from multiplex families suggest a "critical mass" of rare genes is needed for the expression of full syndrome autism. Yet the gender –risk for ASD is substantially higher in males. In addition, recent studies also suggest that neither the severity nor gender of the affected probands predict the risk for ASD in other siblings and first degree relatives (Jacob et al, 2009; Mosconi et al , 2010). This observation suggests that at least for males the vulnerability to ASD may not be determined solely by quantitative threshold effects. This imply a model in which a threshold effect (sufficient number or alleles) or an or epigenetic effects on "Y" or genomically imprinted "X" chromosomes- contributing to gender biases in epidemiological data. This hypothesis also leaves room for the actions of mitochondrial genes, and chromosomal abnormalities such as copy number variants (deletions or duplications) or single nucleotide polymorphisms. These mechanisms point to sources of genetic variability among individuals with ASD. This diversity also provides a mechanism for how some individuals with atypical forms of OCD (including those probands with IDD) may lie on a continuum with the expanded phenotype of ASD (Avramopoulos, 2010; El-Fishaway et al 2011, Ronald et al,2011).

ASD brings several additional developmental issues to the table. Reduced coherence, facial processing deficits and early problems with synchrony and reciprocity of emotional and social communication suggest that ASD differs from OCD and tic disorders in terms of brain structure and function. These differences arise from the regulation of key genes during early brain development and maturation (Novotny et al 2003; Barnhill, 2004, 2005b). In part, ASD is the behavioural expression of an individual adapting to the disruption of embryological and early infant development; OCD, OCSD, tic disorders and secondary forms of while OCD represent later developmental challenges. This hypothesis is consistent with the

observation that insults occurring in utero impact the organization of the CNS rather than functional changes acquired once those systems are in place (Pauls et al, 2002). This observation raises another interesting question. Are infants who are already at risk for ASD more sensitive to post-natal distress that is influenced by aberrant processing facial/emotional stimuli, inability to use synchrony of interaction for self-regulation; difficulty linking pleasure with facial cues; deficits in emotional memory, and severe problems eliciting and responding to mutual or reciprocal social responses (Lerner et al, 2005; Baranek et al, 2007; Feldman et al, 2009)?

These aberrant responses also set up a situation in which neurophysiological differences create a feedback loop in which faulty signaling or aberrant patters of emotional responding fails to elicit appropriate parental responses. This derailment of early development in turn creates a situation in which disturbances in infant-caregiver interactions are analogous to disrupted emotional interchanges (Gunnar, 2007….) The de-synchronization of these critical early attachment behaviours may represent a second potential hit in the development of ASD. In part, this derailment of early mirroring (and activity of mirror neurons) may have an analogue in the adverse effects of maternal depression on infant brain organization and emerging social/emotional and stress/response pathways. The events amplify the adverse effects of infant's genetically at risk for mood disorders (Feldman etc, 2009). To date we have limited data regarding the impact of parents with the expanded phenotype for ASD have on the development of synchrony, reciprocity, joint attention and emerging theory of the mind (Andrews et al, 2003,). It is also unclear what effects parental OCD or Tourette's disorder might have on an infant at genetic risk for behavioral inhibition or the neurocognitive/neurobiological substrates for both disorders (Barnhill, 2005b; Althoff et al, 2010). At a molecular level, these epigenetic effects on key genes may play a key role in the development, penetrance resistence (resilience) to many neuro-psychiatric disorders emergence (Bird et la , 2008; Bucan et al, 2008, Ramocki et al, 2009; Balemans et al, 2010, Stahl, 2010).

IDD plays a major role in the clinical expression and severity of ASD (Novotny et al, 2003). There is also ample clinical evidence that ASD frequently co-occurs with ADHD, tic/obsessive compulsive disorders and mood/anxiety disorders (El-Fishaway et al, 2011). The overlap with ADHD and ASD involves problems with inhibitory controls, executive functions and deployment of attentional resources (Farone et al 2010). Tourette's disorder (TD) and tic-related forms of OCD share increased rates repetitive aberrant social behaviors and attention (inhibition of intrusive thoughts and urges); dysregulation of fronto-striatal-thalamic-frontal circuitry, regulation of dopamine, glutamate and GABA activity; hyper-excitability and changes in refractory periods in the pre-motor cortex (Leckman et al 2003). Mood and anxiety disorders share sensitivities to compromised adaptive skills; temperament associated with behavioral inhibition; several alleles that help regulate neurotransmitter availability; and intracellular regulation of cAMP, kinases/phosphorylases and lipase activity, Brain Derived Nerve Growth Factor (BDNF) and cytokine production; and corticotrophin releasing factors receptor availability and other aspects of neuro-endocrine activity (Post, 2007; Bucan et al, 2008; Avramopoulos, 2010); . These intracellular pathways play a key role in ASD (El-Fishaway, 2010) and OCD (Pauls et al, 2002) but are largely unexplored among persons with IDD and comorbid mental disorders (Barnhill, 2006a; Kiddle et al, 2011).

Many of these systems are also involved in regulating stress response systems. By extension they also affect a child's vulnerability to persistent effects from abuse, neglect and

psychological trauma. For example, the "ss" "sl" alleles in the promoter region of the serotonin transporter protein receptor are associated with an increased vulnerability to trauma (Sugden et al, 2010). They may also play a role in amygdala enlargement, abnormalities in neuronal migration, neurogenesis, synaptic function and regulation of neuro-endocrine responses observed in ASD . The functional activity in Catecholamine- O- Methyltransferase (COMT) (Stein et al, 2006; Albaugh et al, 2010) and regulation of corticotrophin releasing factor production (CRF receptors) (Hiem et al, 2003) also contribute to early brain development play and stress response pathways that eventually be linked to anxiety, PTSD and mood disorders (Gorman 2010). Promoter genes regulating glutamic acid decarboxylase and interneuron development are also associated with a range of neuropsychiatric disorders, epilepsy, and vulnerability to trauma and mood disorders (Barnhill, 2004; Rueda et al, 2007). All influence the link between environmental stress and repetitive behaviors.

The impact of genetic errors on brain development can play out in several directions. One involves regional versus cell-line specific effects. The adverse effects on a cell population arises from defective neurogenesis, insensitivity to trophic factors during early brain development; malfunctioning gene activation/deactivation during neuronal differentiation and maturation; later availability and effectiveness of nerve growth factors and other peptides that maintain as well as protect the integrity and functional viability of neurotransmitter receptors and the intracellular pathways essential for their action. Since most neurons have extensive dendritic interconnections with diverse cell types, developmental errors in neurogenesis, neuron migration and maturation can ramify throughout the developing brain. They are also at the core of many syndromes associated with specific neuro- embryological abnormalities (Barnhill, 2006; Bird et al, 2008; Bagot et al, 2010). Ongoing epigenetic effects, myelination, dendritic neuroplasticity and pruning are triggered by gene activation/silencing. At a structural level these forces shape the neuroanatomical differences between IDD, ASD, tic disorders, OCSD and OCD (Vaccarino et al, 2003). But their greatest long term impact may on the functional integrity and integration of multiple circuits (coherence) (Bagot et al, 2010; Stahl, 2010). As noted earlier, the clinical phenotype of neurodevelopmental disorders is the ever-changing expression of multiple gene-environment transactions. These multi-directional forces are critical to social, emotional, social/emotional communication, and cognitive development(Volpe, 2000; Pomeroy, 2000; Franic et al, 2010). As we have seen, development is a transactional process that relies on neuroplasticity, interactive specialization and integration of multiple brain regions. The gene-environment interactions during early development set the stage and write the script; but epigenetic forces shape all developmental disorders serve as the director and stage manager during the performance and . This metaphor should remind us of the nature-via-nurture model proposed by Ridley (2002) and how this transaction shapes the probability rather than determines the outcome.

11. Conclusions

In this chapter we explored the boundaries of OCD in persons with IDD by comparing and contrasting it with other forms of repetitive behaviors associated with ASD and Tourette's disorder. In particular, this analysis addressed the relationship between OCD and stereotypies/repetitive behaviors in ASD and IDD, OC Spectrum and complex tic disorders. Our review of this relationship generated several questions:

1. How are can we differentiate the impact these developmental disorders from those associated with comorbid mood, OC spectrum disorders and subsyndromal OCD? For example, the co-occurrence of a mood disorders shapes the core anxieties associated with OCD. Hypomania is associated with mood elevation, increased reward seeking behaviors and impaired judgment (Rifkin et al, 2007; Barnhill, 2008b; Bucan et al, 2008). These changes can influence the neuro-behavioral foundation of OCD- change the negative valence of obsessions and/or a shift towards approach rather avoidance or escape functions of compulsions (Barnhill, 2008b).This shift is more consistent OC spectrum disorders. Unfortunately the answer to this question is still a work in progress.
2. Complex tics, OCD and OCSD present with a waxing waning course that can include irritability and worsening of impulse controls. How are these related to mood cycles associated with bipolar disorder? Clinicians can approach these as two distinct phenomena characterized by periodicity. We can distinguish them based on the synchronization of tics and mood-behavior changes (depression increases, hypomania may decrease tic frequency and severity); differentiate irritability associated with a mood disorder from trait-related problems found in many impulse control disorders (as in OCSD); and use genetic and neuroscience data to provide a biological basis for assessing them as independent phenomena (Barnhill, 2005b; Barnhill, 2007b).
3. Is OCD associated with Tourette's syndrome, other neuropsychiatric disorders, bipolar disorder and borderline personality the same condition that co-occurs with social anxiety disorder? In each combination, OCD fits existing diagnostic criteria but the validity of the exclusion criteria that include TD, ASD, or brain disorders is less certain in individuals with severe IDD (King et al, 2007). This blurring of boundaries suggests that both the overlap and specificity of cortico-striatal, limbic and ventral basal ganglia dysfunction may be further muddled by IDD.

As noted, the presence of IDD and ASD makes it decidedly more difficult to answer these questions. These difficulties are often the result of problems encountered in the diagnostic process, especially communication difficulties; impaired understanding of the psychiatric assessment and the capacity to self-report; and sensitivity to catastrophic reactions to disruptions in attachment needs (staff changes) as well as other social and environmental stresses (Fletcher et al 2007). In addition, decreased adaptability associated with IDD and ASD increases the probability that stress will increase the expression of stereotypies, ritual, tics, OC behaviors and ritualized behaviors.

Yet most affected individuals do not present to clinics complaining of depression or troublesome obsessions or compulsions. Most present with a more ambiguous picture of an increase in pre-existing repetitive behaviors- baseline exaggeration (Fletcher et al, 2007). Differentiating these generic behaviors from OCD requires a careful algorithmic approach that is analogous to that used in delineating endophenotypes in research protocols- using both clinical and research data to better differentiate OCD from other repetitive behaviors associated with ASD and severe-profound IDD (Barnhill, 2008). Under these circumstances, it may be more practical to begin the diagnostic paradigm by outlining an endophenotype of repetitive behaviors then progressing to the diagnosis of OCD. Yet to clinicians, this diagnostic paradigm approach might be most useful in the assessment and treatment planning for diagnostic puzzlers or treatment resistant cases.

For the reader, it probably seems practical to exclude these reducing clinical heterogeneity by expanding exclusion and inclusion criteria to include various endophenotypes of repetitive behaviours. The end result of this process is a "purer" form of OCD based on

more specific neurophysiologic, neuroimaging, neuropharmacological and genetic subtyping. Although more time consuming, this approach fine tunes our current system of behavioural observation, rating scales and self-reporting of symptoms (Maitaix-Cols et al 2008). For example OCD could be classified as an anxiety-driven syndrome driven associated with behavioral inhibition, neurophysiological markers of anxiety; specific involvement of the fronto-striatal systems on functional neuroimaging and neuropsychological studies, and neurochemical findings consistent with disruptions in serotonin release and post synaptic action; and an exclusive reliance on compulsions as escape behaviors in the face of internalized conflicts or perceived threats (Zohar et al, 1991; Barnhill, 2008). Even though this endophenotypic approach would tighten the diagnostic rigor for OCD and enhance research studies, there still would be problems adapting such a model by clinicians working with patients who haveS/PIDD (King et al, 2007; Barnhill, 2008) or ASD (Anderson et al. 2004; Schaer et al, 2007; Pauls et al, 2003; Bird et al, 2008; Bucan et al 2008).

Although much work remains several there are several important accomplishments:

1. Laying the groundwork for reframing obsessive compulsive spectrum disorders (including OCD), stereotypies-mannerisms and tic-like behaviors in neurological conditions such as Tourette's disorder as potential endophenotypes of repetitive behaviors.
2. Developing an understanding of repetitive behaviors from a dimensional perspective. Taking this approach reinforces the concept that OCD and repetitive behaviors in persons with IDD/ASD are not easily explained by any single model.
3. Addressing the heterogeneity of OCD in terms of phenomenology and underlying psychobiology, reciprocal social interactions (ethology), interaction between genes and environment in shaping (epigenetics) risk and phenomenology, social-emotional development (infant and childhood development) and learning theory.
4. Synthesizing data from functional behavioral and neuro-psychiatric assessments into a model that integrates brain-behavior with learning models for OCD, OCSD and other repetitive behaviors.
5. Focusing on repetitive behaviors as a final common pathway with multiple etiologies and then addressing the impact of ASD and IDD on these pathways. This model is the centerpiece for defining OCD as an endophenotypes of repetitive behaviors.

In closing, we are back to the basic issues raised at the beginning of this chapter. The eventual solution lies in not only ongoing research but synthesizing current available data into an explanatory rather solely descriptive model. Hopefully we progress beyond the stage of describing, categorizes and quantifying data and focus instead on providing explanations of why this is so. This chapter is but one small step towards such a synthesis.

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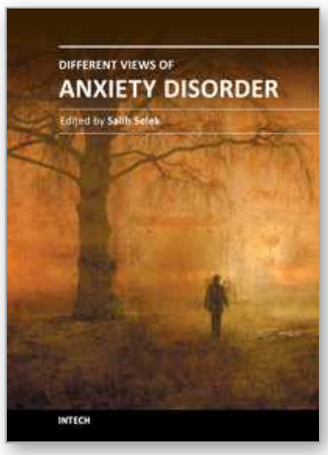

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Anxiety, whether an illness or emotion, is a term with historical roots even in the Bible, but it was not popular until the modern age. Today, we can group, diagnose and treat several anxiety disorders to an extent, but the assessment of symptoms and severity, dealing with resistant conditions, new treatment modalities and specific patient population, such as children, are still the challenging aspects of anxiety disorders. This book intends to present anxiety disorders from a different view and discuss a wide variety of topics in anxiety from a multidimensional approach. This Open Access book addresses not only psychiatrists but also a broad range of specialists, including psychologists, neuroscientists and other mental health professionals.

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