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REVIEW ARTICLE

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A critical review of PANDAS research in the context of obsessive compulsive disorder

The discovery and elaboration of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is emerging from a polemical status and gaining wide recognition. Current research has proposed a specific neurological pathogenesis for the disorder. This paper connects the dominant neurobiological model of obsessive compulsive disorder (OCD) with the proposed pathogenesis and treatment of PANDAS. PANDAS presentation is described and an important early debate regarding anti-neuronal antibodies in the brain of PANDAS patients is outlined. Recent research on a specific immunological trigger for antibodies that cause a blood brain barrier breakdown will be discussed along with treatment for the disorder. Future avenues of research are discussed including a critique of the seminal studies in PANDAS pathology and treatment from the focal point of the dominant OCD model.

KEY WORDS
OCD; immunology; PANDAS; streptococcal bacteria; autoimmune disorder

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BACKGROUND

Obsessive-compulsive disorder (OCD) is characterized by obsessional thinking, and compulsive and repetitive behavior that seeks to decrease the distress caused by intrusive thoughts. OCD affects 1 to 3 percent of the US population, with almost half of these cases having an inception during childhood or adolescence (Kessler et al., 2005). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is an OCD-related disorder initially elucidated by Susan Swedo at the National Institute for Mental Health (NIMH). Children with PANDAS have an abrupt and intense onset of OCD symptoms most often accompanied by motor or vocal tics. This sudden onset of OCD appears to be caused by a common childhood infection, strep throat (i.e., group A beta-hemolytic streptococcal [GAS] pharyngitis). While some children have full remission of symptoms, other children remit considerably and then experience sudden symptoms with even greater intensity following further strep throat infections (Swedo et al., 1998). The OCD symptoms that follow strep throat are also joined by a number of other comorbid symptoms, including anxiety, emotional lability, aggression, and developmental regression (Swedo et al., 2015).

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The relationship between a commonplace infection and a serious psychological disorder has drawn substantial media attention, and only recently has a precise link between OCD and strep throat been elucidated. As validated and replicated research establishing this link has accumulated, PANDAS advocates have sought to advise medical and mental health providers to inform diagnosis and treatment. Reports from the U.S.-based PANDAS Network illustrate the lack of acquaintance with the disorder among medical and mental health professionals. This paper seeks to critically examine the extant literature investigating the PANDAS–OCD neuroanatomical correlates and associated neurobiological models.

OCD ETIOLOGY WITH NEUROIMAGING

The basal ganglia are commonly linked to OCD in neuroimaging studies of children. Within the basal ganglia, the striatum is often implicated, including the caudate nucleus and putamen of the internal capsule and the globus pallidus. The relevant function of these areas includes motivation, reinforcement of behaviors and the interpretation of rewards. In a study of 34 children who were diagnosed with OCD with or without tic disorder following strep throat infections and 84 healthy children, magnetic resonance imaging (MRI) was used to compare any between-group structural abnormalities (Giedd, Rapoport, Garvey, Perlmutter, & Swedo, 2000). The results indicated that the caudate, putamen and globus pallidus were larger in the group of children with OCD and/or tics than the healthy controls. Similarly, a well-cited review of 143 functional neuroimaging studies found that the basal ganglia were often implicated in cases of OCD (Del Casale et al., 2010). The reviewed studies used a number of different techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) and amassed data on 755 patients with OCD.

Voxel-based morphometry (VBM) is a form of neuroimaging that accounts for a number of confounding factors in the intricate comparison of brain scans. In VBM, scans are aligned with a specific prototype that allows for a more detailed analysis between images. In the largest meta-analysis of VBM studies for grey matter changes in OCD, 401 people with OCD compared with 376 healthy controls revealed larger volumes of the putamen and caudate of the basal ganglia in proportion to the symptoms (Radua & Mataix-Cols, 2009). Similarly, a study of 71 OCD patients and the same number of healthy controls revealed an increase in the density of the putamen as well as the thalamus as a correlate related to dysfunction (Yoo et al., 2008).

While the basal ganglia's striatum is often the focus of OCD neuroimaging studies, the thalamus and orbitofrontal cortex (OFC) are also principally implicated and fundamental to neurobiological theories of the disorder. The OFC is a region in the prefrontal cortex that is central to learning and decision-making. The thalamus allows for connections between sensory stimuli and cortical areas. In a review of case reports of brain lesions and OCD from 78 patients, the right portion of the thalamus and the striatum of the basal ganglia were injured in a significant number of these cases (Figee, Wielaard, Mazaheri, & Denys, 2013). Similarly, a review of 755 neuroimaging examinations with patients with OCD demonstrated that a majority had changes in their OFC, and a significant portion had thalamic abnormalities (Del Casale et al., 2010). More support of these anomalies was found in a major VBM review of 511 OCD patients with increased OFC and thalamic grey matter volume in some studies (Piras et al., 2015).

NEUROBIOLOGICAL THEORY AND MODELS

The dominant neurobiological theory of OCD includes the OFC, striatum and thalamus as the core components of the model, known as the orbitofrontal-subcortical or the orbitostriato-thalamocortical model. Though there are some differences in the exposition of these models, depending on the emphasis

on the neurobiological mechanisms, the basic underpinnings of the proposed systems are very similar. Major reviews and meta-analyses of OCD demonstrate the common pathways of the proposed models (e.g. Del Casale et al., 2010; Nakao, Okada, & Kanba, 2014; Piras et al., 2015).

Current models describe an abnormality within the functioning of the striatum, specifically the caudate nucleus, which is a cortical area responsible for goal-directed action (Del Casale et al., 2010). This causes disorganized gating in the thalamus, which serves as a hub of connections between various cortical and midbrain areas. Gating refers to the filtering of certain superfluous connections to avoid an overload or confusion of information. This may lead to excitatory activity in the OFC which is believed to be responsible for OCD's intrusive thoughts (Del Casale et al., 2010). Furthermore, the disorganized gating also may lead to excitatory activity in the anterior cingulate cortex, which is associated with anxiety symptoms and often implicated in anxiety disorders. Del Casale and colleagues (2010) propose that the person afflicted with OCD uses repetitive compulsions as an attempt to effectively regain efficient striatal activity, which may serve to correct the disorganized thalamus and help negate the anxiety in the anterior cingulate cortex. The bypassing of inhibition-related behaviors (i.e., compulsivity) is often attributed to the OFC and thalamus. One study administered fMRI to adolescents who were engaged in a Stroop type task, which sought to bring about self-inhibition of behaviors in relation to certain stimuli introduced by the experiment (Wooley et al., 2008). The results predictably demonstrated decreased activation in the region of the OFC, striatum and thalamus. The medium of behavior reinforcement in the striatum and OFC is found to be serotonin and dopamine release (Maia & Cano-Colino, 2015).

A review of fMRI experiments exploring neuropsychological functions described a variation of the orbitostriato-thalamocortical theory (Nakao et al., 2014). In this variation of the popular model, the OFC is viewed as a "monitor of appropriate behavior in social life" and projects to the striatum and caudate nucleus, which serves as a bridge between the limbic system and the frontal cortex, then into the thalamus as a "filter of information" and back to the OFC (Nakao et al., 2014, p. 597). The imbalance between these pathways causes the caudate nucleus to "lock" and the OFC and thalamus to be hyperactivated, leading to executive dysfunction. The authors cite recent studies pointing to wider aberrations in brain locations related to spatial reasoning and attention. A related review further describes the classic model of OCD as dysfunction in the "orbitofronto-striatal 'affective' circuit"; in other words, OCD is derived from problems with the OFC, anterior cingulate cortex, striatum and thalamus as related to the "emotional and motivational" aspects of behavior (Piras et al., 2015, p. 93). For example, 83% of the studies in this review reported increased volume in the areas associated with the orbitofronto-striatal circuit.

PANDAS PRESENTATION

PANDAS research in the context of OCD

The National Institute of Mental Health (NIMH, 2016) provides five criteria for PANDAS identification:

1. Obsessions, compulsions and/or tic disorders. In a comparison of studies by the NIMH with other research investigations, 60-65% of children were determined to have tic-related comorbidities (Swedo et al. 2015). Further, the most common presentation of OCD symptoms involves phobias and contamination fears, as well as the notorious repetitive behaviors that are associated with compulsions.
2. Pubertal symptom onset. One recent study identifies the mean onset as 7.4 years, or early school-aged students (Murphy et al., 2015).
3. Abrupt onset of symptoms or a relapsing course. The greatest extent of the symptoms takes place within a 24-48-hour window.
4. Association with other neuropsychiatric symptoms. The most common comorbidities are separation anxiety, school issues and hyperactivity (Swedo et al., 2015). Further, emotional lability and somatic symptoms such as sleep disturbance or urinary frequency are frequently comorbid.
5. Association with streptococcal infection. The initial onset could take place months after an infection, but subsequent infections lead to an exacerbation of symptoms. It is notable that the occurrence of PANDAS bears a striking etiological resemblance to the rare Sydenham's chorea (SC), known in the 19th century as St. Vitus' dance. SC is a neuropsychiatric disorder that involves a type of gross and fine motor control loss. This condition manifests in a subgroup of child patients with rheumatic fever following a GAS infection (Van Toorn et al., 2004).

EARLY POLEMICAL RESEARCH ON ANTIBODIES

Following initial findings by Jay Giedd and colleagues, research in the 2000's has focused on the incidence of anti-neuronal antibodies in children with OCD following GAS infection (Giedd et al., 2000). This path of research was meant to determine a causal relationship between strep throat and PANDAS symptoms. One study compared the presence of antineuronal antibodies in PANDAS patients with a control that was only affected by GAS without psychiatric symptoms (Pavonne et al., 2004). Immunofluorescence was

used in this study, a technique useful for the recognition of antibodies. Fluorescent dyes were attached to antibodies after obtaining them from the subject. The antibodies were then reintroduced into a fresh basal ganglia sample that was processed through a centrifuge. Anti-basal ganglia antibodies were discovered in a significant majority of patients in the experimental group relative to the control group. In a similar study, researchers tested for anti-basal ganglia antibodies in patients with OCD and TS, some of which met PANDAS criteria (Morer et al., 2008). This study used techniques other than immunofluorescence, including immunohistochemistry and immunoblotting. While the former technique found none of the antibodies in question, the latter found some presence, though insignificant. The study used putamen samples as opposed to other basal ganglia structures, and this may have limited the results. Further, the authors explain that the results may have been influenced by the sample preparation relative to the intensity of symptom expression. Others have argued that the equivocal findings can be explained by extraneous infection triggers as well as failing to consider other etiologies of OCD and TS in children besides PANDAS (Murphy, Kurlan, & Leckman, 2010).

BREAKTHROUGHS IN PANDAS PATHOLOGY

The investigation of antibodies in the brain of PANDAS patients was expanded to explore cross-reactive anti-GAS antibodies in the basal ganglia of patients with Sydenham's chorea (Kirvan et al., 2006). Cross-reactivity in this case refers to a process in which molecules in the GAS bacterial cell walls actually mimic (or present as similar to) cells that are found in the brain, as well as certain other tissues throughout the human body. This molecular mimicry is thought to be a part of the evolutionary advantage used by ancient *Streptococcus* bacteria for camouflage in the human body (Root-Bernstein, 2014). When the immune response produces antibodies, the target becomes the bacteria as well as the brain tissue itself. In this study, antibodies that reacted to GAS in PANDAS serum were found to provoke CaM kinase II, similar to the proposed pathogenesis of Sydenham's chorea. This effect was not present in children with TS or OCD alone. CaM kinase II is an enzyme that is well established as an important manager of interneuronal signal transmission and is involved in a variety of brain functions including learning and memory (Bejar et al., 2002). Though this proposed mechanism was compelling and replicated in other studies, the actual apparatus that led to antibodies entering the brain was unverified and seen as a major limitation of this hypothesis. Human blood contains a number of infection-related pathogens, but vessels that form a prohibitory blood brain barrier limit their actual access to the brain.

A pivotal study for PANDAS research was a study that linked a specific response to strep throat with a particular T cell response in the nasal-associated lymphoid tissue (NALT) of mice (Dileepan et al., 2011). T cells are types of white blood cells integral in the immune system; their absence is a well-known contributor to deteriorating conditions in HIV/AIDS cases. In this study, mice developed a Th17 response (i.e., a cell that assists the functioning of other immune cells) to repeated intranasal exposure to GAS as a defense against the infection-related pathogens. This particular T cell is also known to lead to autoimmune diseases and inflammatory conditions (Oukka, 2008).

From this breakthrough, a multipart study was conducted (using a model drawn from the role of T cells in multiple sclerosis) to investigate the specific method by which antibodies enter the brain (Dileepan et al., 2016). Initially, the study established that Th17 cells were present in the tonsils of 28 children with GAS infections. Then, using immunofluorescence, the researchers studied the brains of mice with multiple GAS exposures and found that the T cells that were present in their tonsils (i.e., NALT tissue) were also found in their brains. The majority of T cells were found in the olfactory bulb and the anterior olfactory nucleus, the parts of the brain that process the olfactory sensory input. These T cells were also found in areas that connected with the olfactory bulb, including the amygdala and the basal ganglia. Further, they remained in the brains of these mice for over 50 days. In order to test the hypothesis that the T cells derived from the tonsils, and to inversely confirm that blood was not the primary means of transmission of T cells to the brain, the specific protein byproducts (i.e. cytokines) to Th17 were analyzed in the NALT as well as in the brain and determined to be the same. These cytokines (IL-17) were activated after subsequent exposures to the GAS infection. After intravenous injection of the GAS strain that contained these cytokines, no T cells with that particular cytokine profile were discovered in the brain, indicating that the mode of transmission was the NALT.

In the next stage of the experiment, tracers were injected into the blood of the mice to track their movement. The brains were then stained and shown to contain the tracers in the areas of the brain which were inhabited by the GAS specific T cells and their corresponding cytokine profile. This supports the hypothesis that the T cells broke down the blood brain barrier in their respective regions. Research demonstrated that IL-17 creates this breach for patients with multiple sclerosis (Alvarez et al., 2011). After multiple GAS exposures, mice brains were examined to discover neuroinflammation and activation of microglia. Synaptic proteins were observed through immunofluorescence, which showed a significant

reduction in the excitatory information (i.e. vGluT2 proteins) projected into the olfactory bulb by way of the nose (Dileepan et al., 2016).

These important findings provide evidence for a general pathology of PANDAS as well as other CNS autoimmune diseases (Dileepan et al., 2016). Dileepan et al. (2016) synthesized the PANDAS literature and revealed a direct physical link between the GAS bacterial infection and the well-established cross-reactive antineuronal antibodies. Their summative hypothesis posits an entry of antibodies in the blood system of children with PANDAS. Simultaneously, a Th17 response is created in their tonsils as a specific reaction to GAS exposure. When the T cells reach a critical threshold, they move into the brain through the olfactory sensory axons and into the olfactory bulb and its related sites. The inflammatory response that results in the IL-17a cytokines then inflame these brain areas and degrade the blood brain barrier, allowing the problematic antibodies into the brain. Finally, Dileepan et al. (2016) argue that vGluT2 proteins responsible for excitatory neuronal behavior are reduced, leading to dysregulation beginning in the olfactory bulb and transmitting to other regions. The study references a range of neuropsychiatric dysfunctions related to this loss of excitatory proteins and alludes to issues related to the amygdala as possibly explaining the presentation of PANDAS patients. With further infection comes a further expansion of antibodies and cytokines, as well as the relapsing symptoms that characterize PANDAS.

TREATMENT OF PANDAS

Antibiotic use as a prophylactic against further infection significantly improves symptoms in coordination with subsequent infections. One double blind trial took place over a year and compared the course of antibiotics to the previous year's infections and symptoms (Snider et al., 2005). Symptom exacerbation decreased on average by around a .4 SD difference between the baseline year and the study year in the penicillin group along with a similarly significant reduction in strep infections. This study was bolstered by a small pilot experiment that showed marked improvements in the symptoms of children with OCD or tics (Murphy et al., 2015).

Intravenous immunoglobulin (IVIG) is a therapy that has been used to treat a multitude of infectious and autoimmune diseases. IVIG treatment is an injection of collected antibodies from the blood plasma of thousands of donors. The exact reason for IVIG effectiveness is unknown; however, it is popularly theorized that a significant presence of cytokine antibodies is central to the benefits. IVIG has been shown to be effective in treatment of Sydenham's chorea, amongst a host of other antibody-related disorders (Wong & White, 2015). More recently, a double-blind, placebo-controlled study at the NIMH and the Yale Child Study Center (Williams et al., 2016) investigated 35 children with moderate to severe OCD who met PANDAS criteria and were assessed according to the well-recognized Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). All children were prescribed antibiotics (penicillin), and, after receiving treatment in either an IVIG or placebo group, a follow-up assessment was conducted three and six months following the treatment which included phlebotomy and lumbar puncture. Following the double-blind portion of the experiment (at the three-month follow-up), IVIG was administered to all participants, which led to a 49% benefit in symptom severity, including a marked improvement from the three-month point to the six-month point. Although the IVIG group improved symptoms to a higher degree than the placebo group, the double-blind portion of the experiment did not show a statistically significant difference between the IVIG and placebo group. The researchers point to the use of antibiotics in both groups as the presumed reason for this improvement in the placebo group. In addition to these findings, the presence of high amounts of the biomarkers CAM kinase II and ANA titers seemed to predict the greatest improvement in symptoms.

DISCUSSION

Recent research on pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and its link to OCD pathology has important consequences for the practitioner. Increasing awareness of PANDAS, its epidemiology and pathological mechanisms is a central task which can lead to more accurate referral, diagnosis and treatment. For diagnosis, the PANDAS Network, a partner of the National Institute of Mental Health, recommends a specific neuropsychiatric symptom scale based on the work of Susan Swedo (PANDAS Network, 2012). The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is a short yet thorough interview-based assessment that is considered the gold standard in rating the severity of OCD symptoms (Rosario-Campos et al., 2006). An accurate diagnosis of PANDAS and OCD in children and adolescents may involve measures such as laboratory findings and a thorough clinical assessment, and therefore referral to a physician who is aware of PANDAS and related treatment is necessary. In the case of PANDAS, a physician's referral is especially urgent as it will often result in an immediate antibiotic regimen prescribed to fend off reoccurring infection.

The Cunningham Panel was developed to evaluate the aforementioned findings showing a particular set of antibodies in the blood and brains of children with

PANDAS. The Cunningham Panel is a commercially available test that monitors certain antibody markers (e.g., CaM Kinase II) that are present in children who show symptoms of PANDAS exclusively. The test assesses patients according to a likelihood scale that suggests the presence of the disorder. Building on the work of Dileepan et al. (2016), a swab test for T cells with the unique cytokine profile that may penetrate the blood brain barrier might be incorporated into the Cunningham Panel or similar identification measures given the research demonstrating olfactory neurons as a direct pathway for the GAS immune system response traveling to the brain. Empirically valid research incorporating recent developments in autoimmune markers should be incorporated in diagnostic tools.

With regard to research on the treatment of the specific neurological basis of OCD, cognitive behavioral therapy (CBT) in the form of exposure and response prevention (EX/RP) has shown a direct relationship with the OFC loop. Exposure and response prevention involves exposure to imaginary and real-life situations while preventing rituals and compulsions from occurring. The premise of EX/RP is to promote fear extinction by way of exposure, relieving the necessity for the patient with OCD to use compulsions or rituals to alleviate anxiety. In a landmark study that involved positron emission tomography, brain scans of 10 patients with OCD before and after four weeks of intense CBT were taken and significant changes were found in the glucose metabolism of specific areas of their brains (Saxena et al., 2009). Important elements of the OFC loop were affected; that is, thalamic activity was decreased, with a "resultant decrease in thalamocortical excitation" (Saxena et al., 2009, p. 201). Further, the OFC loop's anterior cingulate cortex, well established in relation to fear extinction, showed increased activation in relation to improved symptoms. Saxena et al. (2009) speculated that the presence of medication in patients may have stymied measurable changes in the OFC itself. Zurowski et al. (2012), however, observed 16 unmedicated patients with OCD and measured their response to EX/RP over the course of 3 months using the Y-BOCS scale. Magnetic resonance spectroscopy imaging was performed before and after treatment and compared to determine whether the neurochemistry of the OFC correlated with CBT treatment. OCD patients have been found to have an increased presence of inositol, associated with learning and neuroplasticity, in the OFC. Zurowski et al. found that the level of inositol present in the OFC predicted the treatment outcomes of OCD patients, implying that the OFC is critical in CBT treatment. Further bolstering the involvement of CBT therapy in the OFC loop, Freyer et al. (2011) compared fMRI scans of patients with OCD during a probabilistic reversal learning task (i.e., comparable to the Stroop task) before and after intensive CBT. The study found that there was an increased involvement of the OFC and right putamen, along with decreased symptoms, during the task after the treatment compared to healthy controls.

It is important to reflect on specific and general limitations of the pathway of research discussed in this paper, as well as possible remedies to these limitations. A common limitation of recent PANDAS studies is a lack of replicability. The presence of anti-neuronal antibodies has been well established and constitutes a great deal of the replication research in the decade following Susan Swedo's initial discoveries, but there is a need for further replication studies to rule out variance and provide validation of the most recent research regarding the blood brain barrier, specific biomarkers, and the precise avenue of assault on the brain by the GAS-instigated response.

Limitations of PANDAS treatment research also include a lack of consensus regarding treatment remedies and their hypothesized neurological action. A German case study review found that tonsillectomies had positive outcomes for children with PANDAS, but this may have been a result of post-operative treatment with antibiotics (Windfuhr, 2016). Considering the proposed travel of GAS-specific T cells through NALT after multiple exposures to the bacteria, the efficacy of tonsillectomies should be studied during various intervals, including initial symptoms or repeated infections. Further elucidating the therapeutic benefit of IVIG may be helpful in understanding where to focus research. Though the exact functional basis of IVIG remains unknown, longitudinal, double-blind trials that monitor an array of biomarkers might reveal further antibodies that are important in diagnosis and treatment.

One specific limitation relates to the important work of Dileepan et al. (2016), who did not, in fact, discover widespread damage to the blood brain barrier or plasma deposition in the basal ganglia of the mice in their study despite the presence of T cells in these areas, neuroinflammation in other brain areas (e.g. amygdala) and observations of presumed PANDAS-like abnormal behaviors in the mice. This contrasts with the current research on antibodies that was carried out by observing in vitro antineuronal antibodies in basal ganglia serum (Church et al., 2002). Therefore, the effect of antineuronal antibodies in the basal ganglia, studied in vitro, needs to be reconciled with the aforementioned neuroimaging studies in OCD that reveal structural alterations of volume in the basal ganglia. These limitations suggest a need for further exploration of the mechanism by which anti-neuronal antibodies access and inflame the basal ganglia.

This limitation is also seen in the fact that neuroimaging studies of PANDAS patients exploring volume alteration of the basal ganglia, as opposed to in vitro studies, are not as common as those for OCD

patients without PANDAS (Giedd et al., 2000; Peterson et al., 2000; Swedo & Grant, 2005). Future studies might investigate the breakdown of the blood brain barrier and the mechanism by which the basal ganglia are inflamed, while correlating it with T cell presence in the brain, perhaps by using tracers. Alternatively, a related route of pathology might be pursued. In this respect, the dominant neurobiological explanation of OCD might prove useful. While the OFC may not be reliably compared between human and mice subjects, the lack of abnormalities or blood brain barrier leakage in the thalamus was significant in mice just as it has been described to be affected in OCD patients (Dileepan et al., 2016). As we have seen, functional neuroimaging often reveals volume changes in the thalamus. If blood brain barrier leakage is not the cause of these changes, then monitoring the progression of thalamic change in PANDAS patients might be instrumental in discovering the concomitant changes in the basal ganglia as well. One proposed hypothesis might explore a variation to the proposed thalamic gating mechanism in the orbito-frontal striatal model which leads to dysfunction through the circuit and an impact on the basal ganglia. For example, PET scans of children with PANDAS confirmed precursors to thalamus and basal ganglia inflammation (i.e. activated microglia), but the direct cause was not linked to direct blood brain barrier leakage (Kumar, Williams, & Chugani, 2015). Furthermore, the orbitofronto-striatal model of OCD may need to further incorporate the prominence of the early-inflamed amygdala (Menzies et al., 2008).

As substantial numbers of children continue to struggle with OCD, researchers are making significant strides in understanding the neurological basis, etiology and treatment of this disorder. Susan Swedo's discovery of PANDAS as a particular presentation of OCD has sparked a pathway of research which complements the dominant theory of the etiology of OCD (i.e. the orbitofrontal-subcortical model). Some noteworthy recent trends in research have detailed specific functional abnormalities in the brain, theorized a wholly neurobiological description of the phenomenology of OCD, and traced strep throat bacteria through the nasal cavity and into vulnerable regions of the brain. This paper sought to explore recent developments in the investigation of OCD and PANDAS in children and adolescents with the hope of informing diagnosis and treatment. It is recommended that practitioners who diagnose and treat youth with OCD stay abreast of PANDAS research and consider this potential contributory pathway to the development of OCD symptoms. Incorporating a thorough medical history including questions about recent and prior strep throat infections along with medical consultation may help improve treatment success, such as utilizing an antibiotic regimen in addition to therapeutic interventions.

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