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BIOMARKERS OF ADHD AND ASD: INSIGHT INTO COMORBID ADHD+ASD

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Abstract

Attention-deficit hyperactivity disorder (ADHD) and Autism spectrum disorder (ASD) are two of the most common neurodevelopmental disorders found in children and they show significant symptom overlap. Because both disorders are diagnosed based on behavioral observation, inferring which disorder (or combination of disorders) is causing symptoms in an individual child can be challenging for clinicians, particularly when an individual shows behaviors consistent with comorbid ASD+ADHD. The current study examined resting electroencephalography (EEG), as well as task-related EEG and behavior during a modified flanker task in 50 children (aged 6-12) with either a diagnosis of ADHD (n=17), ASD (n=5), both (comorbid ADHD+ASD, COM; n=8), or no clinical diagnosis (typically developing control, TDC; n=20). EEG and behavioral analyses began by comparing a set of features that have previously been used to discriminate single disorders from TDC. Next, the data from TDC and children with a single diagnosis (ASD-only, ADHD-only) were submitted to *k*-means cluster analysis to evaluate data-driven subgroups regardless of diagnosis. After recovery of the optimal number of clusters (3), the data from COM participants were sorted into the cluster in which they best fit. While none of the regularities found in the literature properly explain the relationships between ADHD, ASD, and COM participants, the use of cluster analysis suggested potential phenotypes that differ in Stimulus Engagement and Feedback Responsivity. These dimensions may have bearing on the efficacy of treatments that target dopaminergic systems, such as methylphenidate. Methods such as these may give insight into the neurobiological underpinnings of an individual's symptoms, which has the potential to guide decisions about appropriate pharmacological treatment and behavioral interventions.

Introduction

Attention-deficit hyperactivity disorder (ADHD) and Autism spectrum disorder (ASD) are two of the most common neurodevelopmental disorders found in children, with prevalence rates of about 9% for ADHD (Danielson et al., 2018) and 2% for ASD (Blumberg et al., 2013). With no genetic or blood tests available to ascertain the presence of these disorders, diagnoses are generally made based on reports from caregivers or clinical observation. However, this proves challenging when attempting to dissociate between ADHD and ASD, two disorders with significant symptom overlap but differing treatment protocols.

The situation is complicated further when a child presents with symptoms of both ADHD and ASD. Prior to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), a diagnosis of ASD precluded a diagnosis of ADHD, with the expectation that any attentional deficits found in ASD were intrinsic to the disorder and not evidence of a comorbidity. With the introduction of the DSM-5, this restriction was removed, allowing providers to diagnose a child as comorbid ADHD+ASD. Unfortunately, many questions remain about the relationship between the two disorders, many of which would be best answered by examining the underlying neurobiology.

Given our inability to examine human neurobiology directly, neuroimaging alternatives such as electroencephalography (EEG) provide a useful proxy. Dense-array EEG allows us to quickly apply many electrodes to the scalp that give insight into the temporal dynamics of an individual's brain activity, either at rest or during the completion of a task. Using EEG, we can examine changes in electrical potentials with millisecond resolution. However, there are tradeoffs: with EEG's impressive temporal resolution comes a lack of spatial resolution. At any given electrode, the recorded potential contains the activity of many different brain regions that

may or may not be actively contributing to task performance. EEG generally requires many trials to compute the average brain activity elicited by a certain stimulus or action, termed an event-related potential (ERP). In theory, this isolates the brain activity that is reliably elicited by a situation because unrelated activity will average to zero and no longer impact the ERP.

Another way to look at EEG is to consider the spectral content, or the amount of power in the waveform that is oscillating at a certain frequency. When used to analyze resting EEG, the average power in each frequency band is generally computed over an entire time period. Alternatively, when faced with task-related EEG, researchers often elect to use time-frequency analysis. This method gives the amount of power in each frequency at each time point, allowing the researcher to examine how much change was induced or evoked by task-related stimulation. Regardless of method, spectral analysis may help ameliorate concerns about data quality in a population that is expected to have increased sensory sensitivity and attentional abnormalities. ERPs contain the average of all activity at a given electrode and given timepoint, while spectral estimates only contain the amount of activity in a given frequency band. This means that while ERPs can simultaneously be biased by slow-moving artifact related to movement and fast-moving artifact related to muscle tension, a spectral estimate will only reflect artifact occurring in the same frequency band. This technique is especially useful when working with children, especially those with sensory or attentional difficulties that may impact data quality, as found in our current study.

ADHD

ADHD is indicated by the presence of pervasive deficits to attention, hyperactivity, and impulsivity in two or more settings that interfere with day-to-day functioning (American Psychiatric Association, 2013). Additionally, to qualify for an ADHD diagnosis, the deficits

must not be symptoms of another disorder and symptoms must begin before the age of 12. ADHD appears to be increasing in prevalence, with 2017 estimates of 9.57% compared to 2011's 8.47% (Zablotsky et al., 2019). The most common treatment for ADHD is medication, with more than 60% of those surveyed reporting pharmaceutical intervention (Danielson et al., 2018; Visser et al., 2014), and 46% engaged in behavioral intervention (Danielson et al., 2018).

The exact mechanisms underlying ADHD (and their causes) are unknown. It is understood that ADHD is a highly heritable disorder (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014) but the effects of environment cannot be understated given the reported efficacy of behavioral treatments (Pelham & Fabiano, 2008). In general, theories of ADHD implicate dysfunction in dopaminergic signaling between the basal ganglia and the cortex that results in inattention, impulsivity, hyperactivity, and altered motivation (Sagvolden, Johansen, Aase, & Russell, 2005). It is noteworthy that animal models and studies of children with ADHD have suggested both a hypo- and hyper-dopaminergic state that may differ across brain regions (Sagvolden et al., 2005), suggesting there may be multiple ways to result in the same behavioral impairment. While the precise nature of altered dopamine functioning in ADHD is unclear, one of the most common and effective treatments is a dopamine reuptake inhibitor, methylphenidate (Storebo et al., 2015). Methylphenidate exerts its effects by blocking the reuptake of dopamine by DAT, increasing the amount of dopamine in the synaptic cleft (Volkow et al., 1998). Use of methylphenidate has been associated with improvements in teacher-reported behavior and parent-reported quality of life (Storebo et al., 2015).

Though not considered part of core ADHD symptomology, research suggests that ADHD may also present with deficits to social cognition. These deficits are often considered the result of primary symptoms of ADHD such as impulsivity and inattention, which compound over time

and lead to social isolation (Leitner, 2014). However, a recent meta-analysis found that using ASD screening tools, 21% of sampled children with ADHD met criteria for a diagnosis of ASD (Hollingdale, Woodhouse, Young, Fridman, & Mandy, 2019). Given that these screening tools look beyond social cognition and include more ASD-specific symptomology such as repetitive and restricted behaviors, this suggests that differences to social cognition found in ADHD may not only be due to downstream effects of ADHD, but due to shared etiology with ASD.

Evidence for shared social symptomology has been found in several tasks. One study found that children with ADHD did not differ from those with Asperger's syndrome, a type of ASD, in their scores on a scale of pragmatic language use (Bishop & Baird, 2001). Children with ADHD were reported to use more stereotyped language and engage in fewer rapport-building communications (Bishop & Baird, 2001), deficits that are more commonly associated with ASD. Similarly, children with ADHD were not distinguishable from those with ASD in their performance on a theory of mind task (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999). A recent meta-analysis of behavioral studies suggested there are deficits to theory of mind and emotion recognition in ADHD relative to TD, particularly regarding recognition of negative emotions (Bora & Pantelis, 2016). However, the impairment in ADHD was not as great as in ASD (Bora & Pantelis, 2016). Taken together, these studies provide evidence of overlap in social symptomology, with the potential for less impairment in ADHD, or restriction to a subsample of those with ADHD.

ASD

ASD is characterized by impairments to social communication and interaction, as well as patterns of restricted and repetitive behaviors (American Psychiatric Association, 2013). These behaviors must present themselves during development and interfere with an individual's day-to-

day functioning to qualify for an ASD diagnosis. Like ADHD, ASD appears to be increasing in prevalence. While only 1.12% of children were reported to have ASD in 2011, 2.49% of children had received this diagnosis by 2017 (Zablotsky et al., 2019). However, it remains a matter of debate whether this increase in prevalence is due to an actual increase in the number of children with ASD or an improved awareness of the symptom profile that allows for greater detection (Zablotsky et al., 2019).

ASD is a highly heterogeneous disorder, with much variation in the symptoms reported and their severity (Masi, DeMayo, Glozier, & Guastella, 2017). Likewise, diverse sets of genes and environmental factors have been identified that may contribute to an ASD phenotype. The prevailing theory suggests that some of these varied causes result in an imbalance of excitatory and inhibitory neurotransmission that culminates in the overt symptomology seen in ASD (Rubenstein & Merzenich, 2003). The diversity of possible effects across multiple domains, including sensory, perceptual, and cognitive, makes this an attractive hypothesis to explain the range of potential symptoms. However, the cause of this disruption, as well as the directionality, remains debated (Dickinson, Jones, & Milne, 2016), and may also suffer from the same heterogeneity.

Treatments for ASD generally consist of behavioral interventions that show the most success if they begin early in life (Koegel, Koegel, Ashbaugh, & Bradshaw, 2014). Applied behavior analysis (ABA) is one form of behavioral intervention that is popular in ASD. ABA uses behaviorist principles of shaping behavior based on feedback to guide the actions of patients (Roane, Fisher, & Carr, 2016). There are no pharmaceutical treatments that cure ASD, but the FDA has approved two atypical antipsychotics, risperidone and aripiprazole, to treat symptoms of irritability in the disorder (Masi et al., 2017). Risperidone acts by blocking certain serotonin

and dopamine receptors (Masi et al., 2017), while aripiprazole modules dopaminergic activity by acting as a D2 receptor agonist or antagonist depending on the amount of tonic dopamine present (de Bartolomeis, Tomasetti, & Iasevoli, 2015). Notably, neither of these drugs target potential mechanisms for the excitatory/inhibitory imbalance thought to be at the core of ASD; they merely treat symptoms.

In addition to the DSM-5 criteria, difficulties with attention are commonly found in ASD. Prior to the DSM-5's allowance for a dual diagnosis of ADHD+ASD, researchers found that more than 50% of studied children with ASD met criteria for ADHD as well (D. O. Lee & Ousley, 2006; Salazar et al., 2015). The frontline treatment for attention difficulties in ADHD is the stimulant methylphenidate, a dopamine reuptake inhibitor, which has been found to be effective at treating attention symptoms in ASD as well (Reichow, Volkmar, & Bloch, 2013). However, administration of methylphenidate in ASD has a smaller effect size than seen in ADHD and potentially increased side effects, including irritability (Reichow et al., 2013). This discrepancy underscores the importance of understanding the biology that gives rise to similar symptoms across disorders. When faced with a child who has been given a dual diagnosis of ADHD+ASD, treating ADHD symptoms with typical ADHD treatments may not be as effective as in a child given a single diagnosis.

Resting EEG

To further understand these disorders, many studies have been performed using EEG, both at rest and during the completion of a behavioral task. One of the most robust resting EEG findings in ADHD research is increased activity in the theta band assessed in frontal electrodes, either calculated independently (Bink et al., 2015; Hermens et al., 2005) or relative to activity in the beta band (Snyder & Hall, 2006). Theta waves are relatively slow, oscillating at 4-7 cycles

per second, and they appear to serve many functions that are task-dependent. For example, increased spontaneous theta activity has been found during mind-wandering accompanied with low alertness (Braboszcz & Delorme, 2011), but induced theta activity has been found in tasks that require conflict resolution or rely on reinforcement learning (Cavanagh & Frank, 2014; Holroyd & Umemoto, 2016). Beta waves are much quicker, at 13-30 cycles per second, and increased power in this frequency band has been found during maintenance of the current state (Engel & Fries, 2010), such as is required during focused attention. A high ratio of theta relative to beta (theta/beta ratio, or TBR) has been found in ADHD, but it has also been found during mind-wandering episodes in adults without the disorder (van Son et al., 2019). This suggests TBR indexes an attention-related state that can occur in all people but may occur more commonly in ADHD.

Increased TBR in ADHD at rest has been considered robust enough that it received FDA approval as a diagnostic biomarker. Studies have found specificity and sensitivity as high as 94% (Snyder & Hall, 2006). However, recent literature reviews suggest that TBR may have declining utility (Arns, Conners, & Kraemer, 2013; Jeste, Frohlich, & Loo, 2015; Saad, Kohn, Clarke, Lagopoulos, & Hermens, 2018). Some recent studies have failed to find differences between typically developing controls (TD) and ADHD, a pattern that may be driven by an increase in TBR in TD (Arns et al., 2013). Others suggest the recent failures may be due to oversampling of a specific ADHD phenotype in previous studies (Jeste et al., 2015), a hypothesis that is supported by a study using cluster analysis that found a distinct high-TBR phenotype (Clarke et al., 2011). Alternatively, it has been suggested that these null results may be due to overdiagnosis of ADHD when another disorder may more appropriately explain attentional symptoms, and that patients with lower TBR may not respond as favorably to typical ADHD treatments (Snyder, Rugino,

Hornig, & Stein, 2015). Taken together, this suggests that variations in TBR may reflect ADHD symptomology, or, alternatively, a specific phenotype within ADHD that may have relevance during treatment selection.

In addition to resting differences in theta and beta activity, researchers have found differences in alpha asymmetry (AS) in ADHD (Baving, Laucht, & Schmidt, 1999; Hale et al., 2010; Hale et al., 2009; Keune, Wiedemann, Schneidt, & Schonenberg, 2015; though null results have been reported, Gordon, Palmer, & Cooper, 2010). To calculate AS, researchers generally compute power at each electrode site, then subtract the natural log of the average power in a left hemisphere electrode (or cluster of electrodes) from the natural log of the average power in a corresponding right hemisphere electrode (Allen, Coan, & Nazarian, 2004). Studies of both children (Baving et al., 1999; Hale et al., 2010) and adults (Hale et al., 2009; Keune et al., 2015) have found greater right hemisphere alpha relative to left. This is generally referred to as "rightward AS." Additionally, children who have a parent with an ADHD diagnosis were found to have significantly greater asymmetry than children of unaffected parents, leading to the suggestion that it may be a marker of genetic load (Hale et al., 2010).

The mechanism underlying alpha symmetry is still debated, and potentially complicated by using a ratio that masks the absolute alpha content recorded from each hemisphere. Some researchers suggest that because alpha is generally inversely related to the underlying cortical activity (Allen et al., 2004), increased right hemisphere alpha in ADHD indicates a hypo-active right hemisphere or hyper-active left hemisphere. The most popular model of AS suggests that hemispheric variations relate to approach-withdrawal motivation (Allen, Keune, Schonenberg, & Nusslock, 2018). In this model, greater left hemisphere cortical activity (and thus lesser left hemisphere alpha) corresponds to a willingness to approach stimuli or situations, while greater

right hemisphere cortical activity (and lesser right hemisphere alpha) mediates withdrawal (Allen et al., 2018). It is possible that differences in motivation found in ADHD may be reflected in this balance.

Further, it has been suggested that rather than simply indicating fewer withdrawal-related tendencies, right hemisphere alpha activity may represent the relative activation of a "behavioral inhibition system" intended to shape motivated behaviors (Gable, Neal, & Threadgill, 2018; Reznik & Allen, 2018). This additional interpretation emphasizes the importance of right dorsolateral prefrontal cortex and right inferior frontal gyrus in cognitive control (Gable et al., 2018). This view suggests that increased right hemisphere alpha may reflect reduced activation of this system and carry with it increased impulsivity and decreased control over motivated behaviors (Gable et al., 2018). A hypoactive behavioral inhibition system would be consistent with ADHD symptomology, namely deficits to impulsivity and cognitive control.

In ASD, on the other hand, of the most common spectral EEG findings is increased power in high beta (20-30 Hz) and gamma (30-80 Hz) frequencies (Edgar et al., 2015; Orekhova et al., 2007; see Rojas & Wilson, 2014; Wang et al., 2013 for reviews). Gamma oscillations are generated through the activity of GABAergic inhibitory interneurons, either in concert with other inhibitory interneurons or driven by excitatory pyramidal cells (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). Alterations to GABA have been found in humans with ASD as well as in animal models. Researchers have used MR spectroscopy to find decreased GABA in the cortices of children with ASD (Gaetz et al., 2014), while others have found increased plasma GABA (Dhossche et al., 2002). Additionally, many of the genes that increase the risk for ASD are involved in coding for GABA receptor subtypes (Coghlan et al., 2012). By comparison, children and adolescents with ADHD have displayed decreased beta activity relative to TD

(Giertuga et al., 2017), though mixed results have been found and some researchers suggest the potential for a high-beta subgroup within ADHD (Clarke et al., 2011). Additionally, children with ADHD have shown decreased plasma GABA relative to those with ASD (Dhossche et al., 2002). Taken together, this suggests that increased high beta/gamma activity while at rest may relate specifically to an ASD phenotype or ASD symptomology.

Just as high beta/gamma appears specific to ASD, TBR may be specific to ADHD. Children with ASD do not appear to have increased TBR as found in ADHD (Chan, Sze, & Cheung, 2007; El-Habashy, Raafat, Afifi, Raafat, & Abdullah, 2016). However, increased rightward AS like that found in ADHD has been found in ASD (Sutton et al., 2005), though a larger study failed to replicate this finding (Burnette et al., 2011). Interestingly, both studies found significant relationships between AS and the expression of ASD: Sutton et al. (2005) found that those with the highest rightward AS scores faced lesser social impairment but greater social anxiety, while Burnette et al. (2011) replicated this finding only in participants with below average IQ. Additionally, Burnette et al. (2011) reported that parents' age of first concern was later in life for children with high rightward AS, leading them to suggest that increased approach tendencies in these children may have masked the presence of their ASD symptoms. While the research that has been performed on AS in ASD has not been as fruitful as that in ADHD, the evidence appears to suggest the presence of functional significance.

Taken together, increased TBR and rightward AS relative to TD may distinguish children with an ADHD diagnosis from TD individuals. Excess TBR would not be expected in ASD, but rightward AS may be present. On the other hand, increased high beta/gamma activity may differentiate ASD from those without a diagnosis, but a subgroup of those with ADHD symptomology may also display this trait.

Behavioral indices and task-related EEG

Reaction times & stimulus-related frontal midline theta

Behavioral studies of ADHD have emphasized measures that relate to cognitive control. Reaction time variability (RTV) is one behavioral measure that appears to consistently differentiate ADHD from TD. ADHD displays greater RTV when making responses across multiple paradigms (Kofler et al., 2013). Potential physiological correlates of this have been found using neuroimaging. A functional magnetic resonance imaging (fMRI) of adolescents with ADHD found their increased RTV related to decreased activation in the caudate and putamen (Rubia, Smith, Brammer, & Taylor, 2007), two basal ganglia structures that are reliant on dopamine signaling, as well as the temporal lobe, thalamus, and cerebellum.

More recently, McLoughlin, Palmer, Rijsdijk, and Makeig (2014), examined EEG using time-frequency analysis to explore the relationship between brain activity and RTV. By looking at the time-frequency contents of the response, rather than an ERP, calculations can be performed on not only the absolute power in a given frequency at a given time, but also intertrial phase coherence (ITPC). ITPC is a measure of phase relationship across trials, with larger numbers indicating greater phase synchrony across trials. McLoughlin et al. (2014) found that ITPC in stimulus-related frontal midline theta negatively correlated with RTV. The authors speculated that abnormalities in frontal midline theta in their study may relate to dopaminergic bursts in the basal ganglia intended to guide action selection that may be altered in ADHD (McLoughlin et al., 2014). Children with ADHD who are treated with methylphenidate show normalized RTV, indistinguishable from those without a diagnosis (Groen et al., 2008). Thus, RTV (and potentially stimulus-related frontal midline theta) may serve as potential markers of unmedicated ADHD that are robust to variations in paradigm.

At the same time, behavioral variability has been found in ASD, with studies reporting increased RTV in ASD relative to TD (Christ, Holt, White, & Green, 2007; Geurts et al., 2008). Despite this, some studies have reported null results (Milne, 2011) or have found that increased RTV in ADHD discriminates participants with ADHD from those with ASD (Groen et al., 2008; Tye, Asherson, et al., 2014). Additionally, Adamo et al. (2014) found that RTV was increased in children with ADHD or ASD with attentional symptoms but not in ASD unaffected by attentional symptoms. These discrepancies have led to the speculation that ADHD symptoms lead to increased RTV in ASD (Adamo et al., 2014; Karalunas, Geurts, Konrad, Bender, & Nigg, 2014). It is possible that examination of RTV on an individual level in children with a comorbid diagnosis would help elucidate the underlying biology.

Other studies of behavior in these disorders have considered the possibility that differences in reaction time (RT) between ADHD and TDC are related to speed-accuracy tradeoff. These hypotheses have sometimes been examined using the drift-diffusion model, which takes a participant's distribution of RTs, generally for a two-alternative forced choice experiment, and fits parameters that explain aspects of the decision process (Ratcliff, 1978). In this model, the participant is assumed to accumulate noisy evidence toward possible decisions. This rate at which a participant accumulates information is called *v*, or drift rate. A response is made when the amount of evidence crosses a decision boundary. The separation between these boundaries is called *a,* and this contains information about the speed-accuracy tradeoff: the larger this parameter, the more information the participant requires to reach a decision, thus the more they emphasize accuracy. The smaller this parameter, the less information the participant requires to decide, thus the more they emphasize speed and disregard accuracy. The final parameter that has been extensively considered in ADHD is *Ter*, or non-decision time. This

parameter includes any time spent encoding the stimulus, extracting relevant features on which to base a decision, and motor execution of the response (Ratcliff, Smith, Brown, & McKoon, 2016).

Results of studies that examine drift-diffusion model parameters in ADHD are mixed. Some studies have found that ADHD can be distinguished from TDC on the basis of *v*, drift rate, or the rate of evidence accumulation, but not *a*, speed-accuracy trade off (Karalunas, Huang-Pollock, & Nigg, 2012; Metin et al., 2013). Others have found significant differences in *a* (Salum et al., 2014), or in T_{er}, non-decision time (Metin et al., 2013; Salum et al., 2014). Taken together, no clear pattern emerges, but it is possible that consideration of drift-diffusion model parameters may give insight into participants' strategy selection.

Sensory EEG

One of the earliest observed features of ASD was altered sensory sensitivity (Masi et al., 2017), though sensory symptoms have only been added to the most recent version of the diagnostic manual (DSM-5; APA, 2013).The amount of sensitivity, and its direction, are both highly heterogeneous: diagnostic criteria accept both hypo- and hyper-sensitivity as potential symptoms (APA, 2013). Studies have found that scores on surveys intended to gauge abnormalities in sensory experience correlate with scores of overall ASD severity (Ashburner, Ziviani, & Rodger, 2008; Sanz-Cervera, Pastor-Cerezuela, Fernandez-Andres, & Tarraga-Minguez, 2015), supporting its relevance to core ASD pathology. Interestingly, these sensory alterations were also found to correlate with scales of inattention, leading Sanz-Cervera et al. (2015) to note the potential that inattention is partially the result of differences in sensory experience.

Within the visual domain, stimulation reliably elicits a series of event-related potentials over occipital cortex, beginning with a positive potential that peaks around 90-100 ms, P1, and followed by a negative deflection called N1 or N170 that peaks between 170-200 ms (Woodman, 2010). These components have been studied in the time-frequency domain and found to reflect an increase in power and phase coherence between 5-15 Hz (Rousselet, Husk, Bennett, & Sekuler, 2007). In ASD, one study examined variability in early sensory response to Gabor patches by computing alpha ITPC in occipital electrodes between 100-170ms post-stimulus onset (Milne, 2011). Participants with ASD showed decreased alpha ITPC relative to TD, as well as increased variability in peak amplitude and latency of the P1. Additionally, peak P1 amplitude variability correlated negatively with RTV on an unrelated task, leading the author to suggest that cortical variability may underlie behavioral variability in ASD (Milne, 2011). It is possible that variability in neural response to stimuli, as assessed by 5-15 Hz ITPC during the time of early visual components, may distinguish participants with ASD from those without.

Another sensory EEG feature that has been suggested to be abnormal in ASD is the N170 to faces. In TD individuals, exposure to faces generally leads to quicker N170 latencies and/or larger amplitudes than other classes of stimuli such as objects or inverted faces, while this is not always found in ASD (Grice et al., 2001; Tye, Battaglia, et al., 2014). The cause of this face/object difference in TD individuals is hotly debated, with some researchers supporting the idea that faces are a special class of stimuli for which human brains have an affinity and thus receive specialized processing in a part of the fusiform gyrus known as the fusiform face area (Rhodes, Byatt, Michie, & Puce, 2004). Others believe these regions merely support expertise, showing increased activation for any class of stimuli with which a participant has great familiarity (Gauthier, 2000). These two interpretations are meaningfully different in the search

for the etiology of ASD: in the former, alterations to the N170 could reflect early sensory deficiencies; in the latter, decreased social motivation could lead to downstream effects on face expertise.

Regardless of the underlying cause of the discrepancy, brain activity during the period of the N170 could potentially be used as a neural signature of pure ASD. The N170 has previously been used to discriminate ADHD and ASD in the laboratory. Tye, Battaglia, et al. (2014) and Groom et al. (2017) found that children with ASD or comorbid ADHD+ASD displayed decreased N170 amplitudes to faces relative to TD or ADHD-only. Additionally, right hemisphere lateralization of the N170 has been found in TD individuals but not in those with ASD (Groom et al., 2017; McPartland et al., 2011) or ADHD+ASD (Groom et al., 2017). Larger N170 amplitudes to faces in TD individuals have been related to increased power and ITPC in a broad frequency range, from 5-25 Hz, with most of the significant differences in power found between 5-15 Hz (Rousselet et al., 2007). Thus, a time-frequency analysis of the difference in power between faces and another class of objects may prove fruitful in examining the neural underpinnings of ASD or ASD symptomology.

Reward anticipation and receipt

Another construct that has garnered much attention in ADHD is receipt of feedback, reward, and punishment. This is not surprising given the reliance of reward signaling on dopamine within the basal ganglia, during which phasic bursts signal the receipt of reward and pauses in tonic firing signal the omission of an expected reward (Schultz, Dayan, & Montague, 1997). Clinical complaints about ADHD often include lack of motivation, particularly for tasks that are not intrinsically rewarding (Hinshaw, 2018), and laboratory studies suggest children with ADHD prefer immediate rewards over delayed more than their TD peers (Demurie, Roeyers,

Baeyens, & Sonuga-Barke, 2012; Scheres, Lee, & Sumiya, 2008; though Scheres, Milham, Knutson, & Castellanos, 2007 found no difference).

One task that gives insight into relative learning from positive and negative feedback is the probabilistic selection task, in which participants must learn to choose "correct" symbols via trial and error. Frank, Santamaria, O'Reilly, and Willcutt (2007) found participants with unmedicated ADHD were impaired at learning from positive feedback relative to TD and ADHD participants taking methylphenidate, while both ADHD groups were impaired at learning from negative feedback. These results are consistent with a hypothesis of altered dopamine-dependent reinforcement learning in ADHD. In unmedicated ADHD, low tonic dopamine may lead to insensitivity to dips in dopaminergic tone that signal the absence of reward, while those taking methylphenidate may have artificially inflated tonic dopamine due to reuptake inhibition.

In all, there is adequate evidence to support feedback-related dysfunction as a marker of ADHD, but neuroimaging studies that attempt to examine the physiological correlates this impairment have yielded mixed results. Studies that looked at brain activity in structures closely tied to reward signaling have found altered patterns of activation in ADHD, including decreased activation in the ventral striatum during the anticipation of rewards (Plichta et al., 2009; Scheres et al., 2007) and increased activation in the caudate nucleus and amygdala that correlated with self-report hyperactivity/impulsivity severity (Plichta et al., 2009). Another study of participants without a clinical diagnosis found that activation in the nucleus accumbens during reward anticipation was negatively correlated with self-report symptoms of inattention (Stark et al., 2011). This suggests that variations in reward anticipation may reflect both inattention and hyperactivity/impulsivity, and that to some extent, symptoms of inattention may lead to deficient error-monitoring processes.

AS has been used as an EEG correlate of reward anticipation, and it has been suggested that tasks that engage relevant circuits may be better suited to discriminate clinical groups from TD than resting data (Stewart, Coan, Towers, & Allen, 2014). One fMRI study found that greater rightward AS, like that found in ADHD, correlated with increased activation in the left anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC) as well as the left orbitofrontal cortex (OFC) during the anticipation of rewards (Gorka, Phan, & Shankman, 2015). This provides supporting evidence that decreased left hemisphere alpha/increased right hemisphere alpha indexes increased neuronal activity in the left hemisphere during reward anticipation.

While studies have not been done to examine AS during reward receipt in ADHD, other constructs that relate to AS have been explored. The error-related negativity (ERN) is a negative-going wave related to dopaminergic error monitoring that is found in frontal electrodes shortly after the commission of an error (Cavanagh & Frank, 2014; Cohen, 2011). The ERN, thought to be generated in the ACC in response to midbrain dopamine signaling (Holroyd & Coles, 2002), has been found to be both smaller in ADHD (Groen et al., 2008) as well as no different (Groom et al., 2010; Jonkman, van Melis, Kemner, & Markus, 2007) relative to TD peers. More relevantly, ERN amplitude has been found to correlate negatively with rightward AS (Nash, Inzlicht, & McGregor, 2012). Given this pattern of results, it would be reasonable to hypothesize that children with ADHD may continue to display increased rightward AS during reward anticipation, and that this continued rightward AS (or failure to modulate alpha activity according to context) may set them apart from TD or those with ASD who are unaffected by ADHD.

In addition to feedback anticipation, there is evidence of altered processing in ADHD during feedback receipt. The feedback-related positivity, another EEG feature thought to be

related to the ACC, is positive-going wave that displays enhanced amplitudes for positive feedback (Holroyd, Baker, Kerns, & Muller, 2008). This potential has previously been characterized as the feedback-related negativity (FRN), a negative-going wave found 200-400 ms after receipt of feedback over frontocentral electrodes that is generally more negative after negative feedback is received (Holroyd & Coles, 2002). In TD individuals who report high behavioral sensitivity, the FRN has been found to correlate negatively with TBR (Massar, Rossi, Schutter, & Kenemans, 2012), suggesting this feature may have some relevance to regularities found in ADHD.

The FRN has yielded mixed results when applied to ADHD, which appear to be context-dependent. van Meel, Heslenfeld, Oosterlaan, Luman, and Sergeant (2011) did not find evidence of a FRN when comparing TD and ADHD children on their receipt of feedback without an associated reward or punishment, nor did Groen et al. (2008) when comparing TD children to those with ADHD or ASD. However, when positive feedback was associated with a monetary gain and negative feedback signaled no gain, TD children displayed an FRN to negative feedback that was not found in ADHD (van Meel et al., 2011). Another study from the same research group found exaggerated FRN amplitudes in ADHD relative to TD (van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005). This suggests that although ADHD does appear to differ in feedback-related potentials, variations in the task used to measure them may influence the directionality (or presence) of group differences. ASD, by comparison, has been shown to have no difference in FRN relative to TD when comparing wins to losses (Larson, South, Krauskopf, Clawson, & Crowley, 2011) or wins to neutral outcomes (McPartland et al., 2012).

Given that the FRN is suggested to be a task-induced theta wave (Cavanagh & Frank, 2014), time-frequency studies of post-feedback theta may serve as an interesting comparison.

Stavropoulos and Carver (2018) found that adults with ASD exhibited less theta power during feedback receipt than TD, regardless of whether they received positive or negative feedback. In a re-analysis of the data used to compare FRN amplitudes in Larson et al. (2011), van Noordt et al. (2017) found that both ASD and TD differentiated between feedback types, with increased theta activity for loss trials relative to win trials during the time the FRN is usually assessed. However, regardless of feedback type, theta ITPC was reduced in ASD (van Noordt et al., 2017). No studies have been identified that examined post-feedback theta in ADHD, but given the abnormalities found in the FRN, it follows that ADHD may display abnormalities in this index as well.

In total, behavioral indices of RTV may differentiate children with ADHD from those without. During a task, stimulus-related early occipital theta/alpha ITPC may differ in those with an ASD diagnosis, and later frontal theta ITPC may differ in those with ADHD. After responses are made, AS may be abnormal in ADHD during feedback anticipation. During feedback receipt, frontal theta ITPC may vary in ADHD, while ASD may differ in early sensory alpha/theta ITPC depending on whether feedback is given in the form of a face or object.

Summary

Taken together, both resting and task-related EEG have been used to differentiate children with ADHD or ASD from those that are TD, but also, in some cases, from each other. The extent to which an individual who has been diagnosed with comorbid ADHD+ASD would fall in line with a typical phenotype was expected to differ.

The current study aimed to (1) determine whether resting EEG and time-frequency indices during a modified flanker task could differentiate children with ADHD, ASD, and comorbid ADHD+ASD; (2a) determine the extent to which the application of *k*-means cluster analysis to behavioral, task-related EEG features, and resting EEG features could discriminate between TD, ADHD, and ASD; and (2b) determine at the individual level whether participants with a comorbid ADHD+ASD diagnosis fit into any of the clusters.

I hypothesized first that (1) ASD would differ from ADHD and TD in resting gamma, early sensory response to stimulus onset, and sensory response differentiation between faces and objects. ADHD would differ from ASD and TD in resting TBR and AS, stimulus-related frontal theta ITPC, AS during reward anticipation, and feedback-related frontal theta ITPC. Specific measures are presented in Table 1, with hypotheses relative to TD for each disorder. Secondly, I hypothesized that (2a) *k*-means cluster analysis would return three clusters that correspond to ADHD, ASD, and TD; (2b) there would be great variability in cluster assignment for those with a comorbid ADHD+ASD diagnosis, with some appearing "more like" one disorder than the other, and some not appearing to fit into a cluster at all.

Method

Participants

Fifty-seven children between the ages of 6-12 with diagnoses of ADHD (n=20), ASD (n=7), both ADHD+ASD (n=10), or no diagnosis (n=20) were recruited to participate in this study. Participants were male except in the ADHD+ASD group, which contained 4 females. Seven participants were omitted from analysis due to an inability to follow procedure (ADHD = 3; ASD = 2; COM = 2), leaving 17 ADHD, 5 ASD, 8 COM (3 female), and 20 TDC that contributed at least one measure for analysis. Details on the reasons for omission can be found in the consort diagram in Figure 1. Demographic information can be found in Table 2.

Participants were recruited from the University of Oklahoma Health Sciences Center's Child Study Center, as well as via mass mailing, local message boards, and other area pediatric clinics. ASD diagnoses were confirmed via score above threshold of 15 on the Social Communication Questionnaire (SCQ; Rutter et al., 2003), a common screening tool for ASD, confirmed diagnosis by a clinical psychologist or medical doctor, and document review by a licensed medical doctor with experience in ASD diagnosis. ADHD diagnoses were confirmed via review of the parent and teacher Vanderbilt Diagnostic Rating Scales (Vanderbilt; Wolraich et al., 2003) as well as review of documentation by a licensed medical doctor with experience in ADHD diagnosis. Children with a comorbid diagnosis of ADHD+ASD scored in the affected range on both scales and have adequate documentation to support a dual diagnosis. Typically developing (TD) children had scores below threshold on both the SCQ and Vanderbilt, as well as no history of diagnosis. Prior to completing the EEG, potential participants completed the Kaufman Brief Intelligence Test (KBIT; Kaufman & Kaufman, 2004) and the SCQ. Participants without a diagnosis of ADHD additionally completed the Vanderbilt. Participants with a comorbid diagnosis

of ADHD+ASD additionally completed the Vineland Adaptive Behavior Scales (VABS; Sparrow, Cicchetti, & Balla, 2005), which assesses how well the participant completes activities of daily living, and Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 2007), which tests the participant's receptive use of language.

Exclusion criteria were nonverbal IQ and verbal IQ both < 70; presence of a seizure disorder or known pathogenetic disorder; history of multiple concussions or traumatic brain injury; or current use of any psychotropic medication aside from stimulants. Participants prescribed stimulants were asked to refrain from use for 48 hours prior to the study session to allow for medication washout. Eligible participants who were TD or had a single diagnosis of ADHD or ASD received $40 for their participation; participants with a comorbid diagnosis received $60 for their participation due to an increased number of scales administered. Children were additionally allowed to pick a small prize from a toy box after the completion of the EEG.

Group differences in demographic variables were examined using a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) ANOVA.

Setting

Participants were met at either the Child Study Center (Oklahoma City, OK), Early Foundations (Oklahoma City, OK), or the OU Brain and Biomarker Laboratory (Norman, OK) at their convenience. Surveys and questionnaires were completed in a well-lit office or conference room. Upon their completion, participants were taken back to a dimly lit room previously screened for electrical artifact and familiarized with the EEG equipment and experimental laptop.

EEG recording & processing

Participants were fitted with a 128-channel saline-based HydroCel Geodesic EEG Net (HCGSN; Electrical Geodesic, Inc, Eugene, OR). At the beginning of the session and between tasks, impedance values were adjusted until < 50 kΩ. EEG was sampled at 1000 Hz, recorded unfiltered, and referenced to Cz during acquisition.

Procedure

Rest. As soon as the EEG net was adequately applied, participants engaged in a period of guided rest for 3 minutes. Following the experimenter's direction, participants sat quietly with eyes open for 1 min, followed by 30 s of eyes closed, then another 1 min of eyes open, followed by another 30 s of eyes closed. Participants always completed the rest portion of the study prior to beginning the task.

Flanker task. On each trial, participants viewed an array of five characters that appeared on the screen for 200 ms. Stimuli were arrows placed in the center of the screen, with one target stimulus in the form of "<" or ">" appearing in the center and two adjacent distractors on each side that were either the same as the target stimulus (congruent; for example, "<<<<<") or different (incongruent; for example, "<<><<"). Participants were instructed to sit quietly in front of the laptop screen with their left forefingers resting on the left CTRL button and right forefingers on the right CTRL button. Participants were instructed to use the keyboard to indicate the direction of the target stimulus as quickly as possible, and to ignore the distractors that would try to trick them. See Figure 2 for example stimulus arrays.

After response or termination due to nonresponse, a 1500 – 2500 ms delay occurred before valid feedback was given for 500 ms in the form of a happy face (social, positive) or check mark (nonsocial, positive) in the event of a correct answer, or sad face (social, negative) or

X mark (nonsocial, negative) in the event of an incorrect answer. Nonsocial feedback stimuli were created via scrambling the faces to roughly equate the amount of visual information presented across trial types. If no response was received for 4000 ms, negative feedback was given. An intertrial interval between 1000 and 2000 ms occurred between the offset of feedback and the onset of the next trial. Participants completed 10 practice trials and gave affirmation that they understood the task. Practice was repeated until the participant was comfortable with task instructions. Participants completed 1-2 blocks of 100 trials dependent on willingness to continue.

Stimuli were presented using Presentation (Neurobehavioral Systems, Inc.) on a 38 cm x 21.6 cm widescreen LCD laptop screen with a display resolution of 1920 x 1080. Target arrays were generated using 20-point Geneva font. Feedback stimuli were sized 424 x 640, or 8° × 12° visual angle. Participants were seated approximately 60 cm from the laptop screen.

EEG processing

Raw resting data were examined in EEGLAB 13 (Delorme & Makeig, 2004) for Matlab (The Mathworks, Natick, MA). Data were digitally filtered from .5 Hz (12 db/octave rolloff; zero-phase) to 120 Hz (24 db/octave rolloff; zero-phase), and notch filtered at 60 Hz. Segments of excessive artifact and individual bad electrodes were removed. Blinks, saccades, heart rate, and muscle artifact were removed using independent component analysis. Due to the short duration of the resting files, principle components analysis (PCA) was used to reduce the number of components to 16 prior to independent components analysis. After artifact removal, removed sensors were added back to the data via spherical spline interpolation. No more than 5% of electrodes were interpolated per subject and care was taken to ensure spatially adjacent clusters were not interpolated. Resting data were segmented into 2 s epochs and submitted to a fast

Fourier transform in Matlab with 50% overlap. Abnormal linear trends were identified in the data by fitting a straight line to each electrode on each trial. Trials in which a line fit an electrode with a slope of > 50 μV and an R^2 > .30 were rejected from the data, as were trials that contained amplitudes greater than 75 μV or less than -75 μV. Participants with 15+ clean resting epochs were retained for analysis.

Because alpha activity varies with age (Aurlien et al., 2004), each participant's alpha band was estimated by comparing his or her power spectral density during eyes-open segments with that from his or her eyes-closed segments and finding the largest peak between 8–13 Hz. Individual alpha bands were constructed from -2 to +2 Hz around the peak frequency and used for resting and pre-feedback AS. Individual theta bands were also generated using the window -6 Hz to -3 Hz below peak alpha frequency, similar to methods previously used to characterize theta for TBR comparisons in ADHD (Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011).

Raw task-related data were examined in BESA 6.0 (MEGIS Software, Grafelfing, Germany). Segments of excessive artifact were removed, and bad electrodes were interpolated using spherical spline interpolation. No more than 5% of electrodes were interpolated per subject and care was taken to ensure spatially adjacent clusters were not interpolated. Data were digitally filtered from .5 Hz (12 db/octave rolloff; zero-phase) to 120 Hz (24 db/octave rolloff; zero-phase), and notch filtered at 60 Hz. Blinks, saccades, heart rate, and muscle artifact were removed using independent component analysis in EEGLAB 13 (Delorme & Makeig, 2004) for Matlab. Data were re-referenced to the average of all sensors and Cz, the reference electrode, was recreated. There were three participants who completed the task but did not provide usable resting data. To gauge these participants' peak alpha frequencies, a fast Fourier transform was

calculated on his or her entire cleaned task-related dataset. The largest peak between 8-13 Hz was chosen as the participant's peak alpha frequency.

Statistical analysis

Prior to analysis, values that were +/- 3 SD from the sample mean were removed from the dataset. Follow-up tests used Tukey's HSD where appropriate.

Resting frontal TBR

Resting TBR was assessed in electrode Cz by calculating the ratio of absolute theta to absolute beta (13-30 Hz). Theta frequencies were calculated individually for each participant by using the window -6 to -3 below peak alpha. The beta band did not vary by individual. Despite the inherent difficulties that come with using single electrodes, only Cz was utilized due to its prevalence in the ADHD literature (Arns et al., 2013) and the promotion of TBR in Cz as a single-electrode diagnostic aid (Snyder et al., 2015). See Fig. 3. for the location of this electrode, circled in thick black. The resultant value was submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of an ASD diagnosis) ANOVA.

Resting frontal AS

Resting frontal AS was assessed by taking the natural log of absolute alpha power in a small cluster of three electrodes including F7 (HCGSN electrodes 33, 27, 34) and F8 (HCGSN electrodes 122, 123, 116). See Fig. 3, highlighted in red. Each participant's alpha band was individually constructed to vary -2 to +2 Hz around his or her peak alpha frequency. Mean power in the left hemisphere was subtracted from power in the right, then normalized by the total alpha power in those electrodes. The resultant value was submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of an ASD diagnosis) ANOVA.

Resting central high beta/gamma

Resting absolute high beta/low gamma (20-50 Hz) was measured in a cluster of 5 electrodes including Cz (HCGSN electrodes 129, 7, 106, 31, and 80). See Fig. 3 for the locations of these electrodes, highlighted in orange. Because increased gamma in ASD has been found to be topographically widespread (Orekhova et al., 2007), electrodes were used that were least likely to be contaminated by movement or muscle artifact. The resultant value was submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of an ASD diagnosis) ANOVA.

Behavior

Behavior was examined for participants that completed at least one full block of 100 trials. All behavioral estimates were made using only the first 100 trials due to variations in participant compliance and stopping point. Accuracy was assessed by considering the number of correct responses for each of 50 congruent and 50 incongruent trials, as were errors of omission. Participants with values +/- 3 SD of the mean were removed as outliers. There were no outliers removed from the accuracy comparison. Two participants from the ADHD group were removed for having excess errors of omission in the congruent condition; one participant with ADHD was removed for having excess errors of omission in the incongruent condition. Accuracy and errors of omission were separately submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (congruent/incongruent) repeated measures ANOVA.

Ex-gaussian distribution parameters

Estimates for mu, sigma, and tau were generated using the DISTRIB toolbox (Lacouture & Cousineau, 2008) for Matlab, which began with reasonable estimates based on the gaussian parameters of the data and used a simplex method implemented by fminsearch to find optimal

parameters to describe the distribution. Participants were omitted from this comparison if the log likelihood value returned as -Inf due to extremely small values of tau and lack of ex-gaussian shape (n=7). Each pair of values was examined using a 2 (presence of ADHD diagnosis) x 2 (presence of an ASD diagnosis) x 2 (congruent/incongruent) repeated measures ANOVA.

Diffusion model

To test predictions related to speed-accuracy tradeoff, every participant's mean RT, variance, and accuracy were submitted to the EZ-Diffusion model (Wagenmakers, van der Maas, & Grasman, 2007) separately for congruent and incongruent trials. This model is similar to the complete drift-diffusion model proposed by Ratcliff (1978), but it is vastly simplified; rather than allowing these parameters to vary across trials, one estimate is returned to explain the individual's entire distribution. It also does not allow the participant's starting point to vary: the diffusion process is constrained to begin halfway between the boundaries, which does not allow for estimation of bias. However, it is similar in that it returns estimates of *a, v,* and $T_{er,}$ which provide the necessary information to make judgments about speed-accuracy tradeoff.

Per the recommendations of Wagenmakers et al. (2007), participants with 100% accuracy were submitted with an accuracy value that included half of an error, or 99%. Per further recommendations of Wagenmakers et al. (2007), distributions were checked for non-normality using D'Agostino's *k*, and those whose RTs were not statistically non-normal were excluded from analysis (n=27). Additionally, participants with values of non-decision time, T_{er} that were biologically implausible (negative values; n=2) were omitted. Finally, participants with chance or below chance accuracy were excluded, as the model would not run with chance accuracy (n=2) and returned implausible values for drift rate, *v*, when accuracy was below chance (n=2).

These restrictions left a sample of 15 participants, for which each diffusion model parameter was examined separately using a 2 (presence of ADHD diagnosis) x 2 (presence of an ASD diagnosis) x 2 (congruent/incongruent) repeated measures ANOVA.

Stimulus-related frontal theta ITPC

Stimulus-related epochs were generated from 1000 ms prior to stimulus onset to 1000 ms after. Trials with amplitudes greater than 120 μV were removed. ITPC was computed using Morlet wavelets with 1 Hz frequency steps using a cycle length that increased linearly from 1 cycle at the lowest frequency (2 Hz) to 10 cycles at the highest frequency (40 Hz). ITPC was down-sampled to 250 time-bins. ITPC values were corrected by subtracting the critical r value, calculated as sqrt[-1/(number of trials)∗log(0.5)], based on each participant's trial count to remove the correlation between trials expected by chance. Mean theta ITPC was calculated between 200 – 400ms post stimulus onset in four electrodes including and posterior to Fz (HCGSN 5, 6, 11, 12). See Fig. 3 for electrode locations, highlighted in gray. Participants with 15+ trials were retained for analysis, which will consist of a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) ANOVA.

Stimulus-related occipitoparietal theta/alpha ITPC

Stimulus-related epochs used for estimation of frontal theta were also used to calculate theta/alpha ITPC in two occipitoparietal clusters, consistent with the literature (Rousselet et al., 2007). Left hemisphere electrodes included P7 (T5, HCGSN 58) and neighboring 59, 64, and 65; right hemisphere electrodes included P8 (T6, HCGSN 96) and neighboring 90, 91, and 95. See Fig. 3, highlighted in blue. The original intent was to examine neural activity between 5-15 Hz during the time period between 140-240 ms post-stimulus onset, to coincide with typical N170

latencies and to replicate previous work in adults (Rousselet et al., 2007). However, review of the group mean ITPC plot suggested that these windows would not adequately capture the visual response in these children/adolescents, so 3-10 Hz between 75-300 ms post-stimulus onset was instead examined to capture low frequency peak neural activity. This resulted in two ITPC estimates for each participant that differed only by hemisphere (left vs right). Participants with 15+ trials were retained for analysis, which consisted of a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (hemisphere: left/right) repeated measures ANOVA.

Pre-feedback frontal AS

Feedback-related epochs for correct trials were generated from 1500 ms prior to feedback to 500 ms after feedback onset. Trials with amplitudes greater than 120 μV were removed. Event-related spectral perturbation (ERSP) was computed using Morlet wavelets with 1 Hz frequency steps using a cycle length that increased linearly from 1 cycle at the lowest frequency (2 Hz) to 10 cycles at the highest frequency (40 Hz), then down-sampled to 250 time-bins. The natural log of each participant's individual average alpha band power in three left hemisphere electrodes including F7 (HCGSN electrodes 33, 27, 34) was subtracted from the natural log of his or her average alpha band power in three right hemisphere electrodes including F8 (HCGSN electrodes 122, 123, 116), then normalized by dividing by the mean alpha power in those electrodes. See Fig. 3 for electrode locations highlighted in red. Participants with 15+ trials were retained for analysis using a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) ANOVA.

Post-feedback frontal theta ITPC

Feedback-related epochs for each of two feedback types (social-positive; nonsocial-positive) were generated from 1000 ms prior to feedback onset to 1000 ms after. Trials with amplitudes greater than 120 μV were removed. ITPC and ERSP were computed using Morlet wavelets with 1 Hz frequency steps using a cycle length that increased linearly from 1 cycle at the lowest frequency (2 Hz) to 10 cycles at the highest frequency (40 Hz). ITPC and ERSP were down-sampled to 250 time-bins. ITPC values were corrected by subtracting the critical r value based on each participant's trial number to remove the correlation between trials expected by chance. Mean theta ITPC occurring 200 – 400ms post feedback onset in four electrodes including and posterior to Fz (HCGSN 5, 6, 11, 12) were identified for each trial type, in accordance with previous literature (van Noordt et al., 2017). See Fig 1. for electrode locations, highlighted in gray.

Participants with 15+ trials in each category were retained for analysis, which consisted of a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (sociality: social/nonsocial) repeated measures ANOVA.

Post-feedback occipitoparietal theta/alpha power

Event-related synchronization (ERS): Feedback-related epochs used for estimation of frontal theta were also used to calculate theta/alpha power in two occipitoparietal electrode clusters, consistent with the literature (Rousselet et al., 2007). Left hemisphere electrodes included P7 (T5, HCGSN 58) and neighboring 59, 64, and 65; right hemisphere electrodes included P8 (T6, HCGSN 96) and neighboring 90, 91, and 95. See Fig. 3, highlighted in blue. The original intent was to examine mean theta/alpha power between 5-15 Hz during the time period between 140-240 ms post-stimulus onset, to coincide with typical N170 latencies. However, like the visual response to stimulus onset, review of the data suggested that these

parameters would not capture the response in these children/adolescents. Instead, power was examined between 3-10 Hz from 75-300 ms and baseline corrected using the time period between -100 and -500 prior to feedback onset. ERSP was only used from correct feedback trials because of increased likelihood the participant is attending to the screen. This resulted in four scores that varied by hemisphere (left/right) and sociality (social-faces/nonsocial-checks). Participants with 15+ trials in each condition were retained for analysis. Analyses included a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (hemisphere: left/right) x 2 (sociality: social/nonsocial) repeated measures ANOVA.

ERS ratio: A change score was generated by subtracting power for checks from power for faces then dividing by the power for faces, which resulted in two normalized spectral power estimates that vary by hemisphere (left/right). ERS ratios were submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (hemisphere: left/right) repeated measures ANOVA.

Event-related desynchronization (ERD): In addition to the power increases seen in occipitoparietal electrodes post-feedback onset, there was also a clear period of desynchronization later and in higher frequencies. This was examined in an exploratory analysis between 10-15 Hz, from 300-550 ms post feedback onset, in the same electrode clusters as the ERS. This resulted in four scores that varied by hemisphere (left/right) and sociality (social: faces; nonsocial: checks). Participants with 15+ trials in each condition were retained for analysis. Analyses included a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (hemisphere: left/right) x 2 (sociality: social/nonsocial) repeated measures ANOVA.

ERD ratio: A change score was generated by subtracting power for checks from power for faces then dividing by the power for faces, which resulted in two normalized spectral power

estimates that vary by hemisphere (left/right). ERD ratios were submitted to a 2 (presence of ADHD diagnosis) x 2 (presence of ASD diagnosis) x 2 (hemisphere: left/right) repeated measures ANOVA.

k-means cluster analysis

All behavioral, event-related, and resting EEG measures for TD, ADHD, and ASD were converted to *z* scores based on the means and standard deviations of TDC and submitted to *k*-means cluster analysis implemented in R, which allows for missing data. This algorithm partitions the data into a user-specified number of clusters by first beginning with randomly chosen datapoints that serve as "centroids" for each cluster. With each iteration, data points are assigned to a cluster and the centroid is adjusted to reflect the mean of that cluster. The algorithm continues with the goal of minimizing within-cluster variability until the requested number of iterations is complete or the centroid value no longer changes. After clusters are assigned, silhouette plots can be generated that show the similarity between each participant and its cluster. The strength of this analysis lies in its ability to encapsulate all the potential markers of each disorder in one analysis, letting the data speak to which markers are relevant to classification and which are not.

The cluster analysis began with three groups that were expected to reflect TD, ASD, and ADHD, while also allowing for the possibility that only two clusters or up to ten clusters would result. After recovery of a stable number of clusters, data from the comorbid ADHD+ASD participants were submitted for classification. That is, their own *z*-scored variables were classified into the cluster they are closest to by minimizing the distance between cluster means and their own data. This allowed us to determine the cluster to which their brain activity is most

closely related. Follow-up analyses compared clusters on variables that may affect classification such as age, IQ, and disorder symptomology.

Given the variability found within ADHD when using cluster analysis (Clarke et al., 2011), and the symptom variability found in ASD, it was not unlikely that more than one cluster may be found for each disorder. Exploratory analyses relied on visual inspection of the resultant silhouette plot that displayed how similar participants were to their own clusters (individual difference scores from the cluster mean) relative to other clusters, as well as comparison of mean silhouette scores and percent variance accounted for by each cluster. Elbow plots were also generated which plot the sum of squared distances between cluster members and their cluster means for each number of clusters, with an expected "elbow" in the plot as increasing cluster numbers provide diminishing returns for reducing cluster distances. The value at the bend of the elbow is considered to be the optimum number of clusters. Together, these sources of information were used to identify the number of clusters that explained the most variance while maximizing within-cluster similarity. Again, participants with a comorbid ADHD+ASD diagnosis were submitted to these data-driven clusters post-hoc to determine where best they fit.

Discriminant analysis

After clusters were generated and comorbid participants were sorted into a cluster, linear discriminant analysis was used to further understand the contribution of each variable to cluster membership. This analysis considers the entire dataset of continuous variables, as well as the categorical cluster membership, and generates *k*-1 linear functions that best predict cluster membership. This technique reduces the dimensionality of the data from a scattershot list of variables to an interpretable set of maximal differences. Because this analysis required a complete dataset, missing values were replaced with their cluster's mean for that variable. This

necessarily reduced within-group variability and increased discriminability between clusters. However, this approach was considered preferable to imputation due to the relatively small sample size and myriad dimensions that could be considered to generate realistic replacement scores. Complete details on the pattern of missing data across clusters can be found in Table 3.

Results

Demographics

Full ANOVA results for demographic comparisons by diagnosis are found in Table 4.

Age: Participants ranged in age from 6-12 years old ($M = 9.08$, $SD = 2.03$). Age did not differ based on ADHD diagnosis or ASD diagnosis.

IQ: K-BIT nonverbal IQ ($M = 102.65$, $SD = 17.70$) did not differ based on ADHD diagnosis, or ASD diagnosis.

SCQ: As expected, there was a significant effect of ASD diagnosis on SCQ score but not ADHD. A post-hoc Tukey test showed that participants with an ASD, either alone or comorbid with ADHD, had significantly higher SCQ scores ($M = 20.70$, $SD = 5.39$) than those without ($M = 4.03$, $SD = 4.26$).

Peak alpha frequency

Peak alpha frequency ranged from 8-12 Hz ($M = 9.47$). There were no effects of ADHD, $F(1, 46) = .62$, $p = .43$, or ASD diagnosis, $F(1, 46) = 1.72$, $p = .20$, on peak alpha frequency. Peak alpha frequency correlated significantly with age, $r = .32$, $p = .03$.

Resting frontal AS

There were no significant effects of ADHD or ASD on resting AS. Full ANOVA results for resting comparisons by diagnosis are found in Table 5.

Resting frontal TBR

There were no significant effects of ADHD or ASD on resting TBR.

Resting central high beta/gamma

There were no significant effects of ADHD or ASD on resting gamma.

Behavior

Full ANOVA results for behavioral comparisons by diagnosis can be found in Table 6.

Accuracy: There was a significant effect of congruency, with more correct trials in the congruent condition (M = 43.13, SD = 7.89, or 86% accuracy) than the incongruent condition (M = 33.10, SD = 10.66, or 66% accuracy). There was a trend toward ADHD producing more errors overall but this comparison did not attain significance. There was no significant effect of ASD nor were there any interactions (all ps > .50).

Errors of omission: There was a significant main effect of ADHD, such that participants with an ADHD diagnosis made more errors of omission (M = 3.11, SD = 2.52) than those without an ADHD diagnosis (M = 1.25, SD = 1.34) during the first block of trials. There were no effects of congruency or ASD, nor were there any interactions (all ps > .10).

Ex-gaussian distribution parameters

Tau: Participants with a diagnosis of ADHD had significantly larger tau parameters but there was no effect of ASD. There was also a significant effect of congruency, such that tau

increased in the incongruent condition (M = 372.94) relative to the congruent condition (M = 294.25). There were no interactions between diagnoses and congruency (ps > .2).

Mu: Mu did not differ according to ADHD diagnosis or ASD diagnosis. There was a significant effect of congruency, such that mu was larger for the incongruent condition. There were no interactions between diagnoses and congruency (ps > .65).

Sigma: Sigma did not differ according to ADHD diagnosis or ASD diagnosis. There was a significant effect of congruency, such that sigma was larger for the incongruent condition. There were no interactions between diagnoses and congruency (ps > .55).

Diffusion parameters

a (boundary separation): There was a trend toward a relationship between congruency and *a*, and a trend toward an interaction between congruency and ASD. While on average the sample had larger values of *a* for the incongruent condition, the three participants with an ASD diagnosis considered in this comparison had similar values across conditions. There were no main effects of ADHD or ASD.

v (drift rate): There was a significant relationship between congruency and *v*, such that larger values of *v* were obtained for the congruent condition than the incongruent condition. There were no significant effects of ADHD, or ASD, nor were there any interactions between diagnosis and congruency (all ps > .7).

T_{er} *(non-decision time):* There was a significant relationship between congruency and T_{er}, and a trend toward an interaction between ASD and congruency. While most of the sample had larger values of T_{er} for the incongruent condition, the three participants with an ASD diagnosis in

this comparison had an attenuated difference between conditions. There were no main effects of ADHD or ASD, and there was no interaction between ADHD and congruency.

Stimulus-related frontal theta ITPC

There was a trend toward an effect of ADHD on stimulus-related frontal theta ITPC, such that participants with ADHD had reduced ITPC (see Fig. 4). There were no effects of ASD. Full ANOVA results for task-related EEG comparisons can be found in Table 7.

Stimulus-related occipitoparietal theta/alpha ITPC

There were no effects of ADHD diagnosis, ASD diagnosis, hemisphere, or interactions (all *p*s > .35) on stimulus-related occipitoparietal theta/alpha ITPC (see Fig. 5).

Pre-feedback frontal AS

There were no effects of ADHD diagnosis, or ASD diagnosis on pre-feedback frontal AS.

Post-feedback frontal theta ITPC

Participants with ASD had significantly greater post-feedback frontal theta ITPC across conditions, but there was no significant effect of ADHD diagnosis (see Fig. 6). There was also no effect of sociality; overall, both happy faces and checks elicited roughly the same ITPC. There were no interactions between sociality and diagnosis (all *ps* > .25).

Post-feedback occipitoparietal theta/alpha power

ERS: There was a significant relationship between feedback sociality and post-feedback power estimates such that checks elicited more baseline-corrected power than happy faces. There was also a significant interaction between hemisphere and ASD diagnosis, with participants with an ASD diagnosis displaying greater left hemisphere power across feedback types, as well as a

trend toward an interaction between sociality and hemisphere. There were no main effects of ASD or ADHD, nor was there a main effect of hemisphere. There were no other interactions (all *p*s > .10). See Figures 7-10 for plots of each condition in each hemisphere.

ERS ratio: Examining ERS as a ratio of trial types (happy face - check / happy face) found a significant main effect of ADHD, such that ADHD had more negative ratios in both hemispheres. Given that the ratio is intended to identify the amount of additional activity induced for faces, a more negative number suggests increased brain activity in response to checks. There was no effect of ASD or hemisphere, nor were there any interactions (all *p*s > .5).

ERD: There was a significant main effect of hemisphere, such that greater desynchronization occurred in the right hemisphere. There were no effects of ADHD, ASD, or feedback sociality. There were no interactions (all *p*s > .45).

ERD ratio: There was a trend toward a main effect of ADHD, with ADHD having more negative ratios and thus displaying increased desynchronization for checks relative to faces. There was no main effect of ASD, or hemisphere, nor were there any interactions (all *p*s > .20).

k-means cluster analysis

A subset of the variables was selected for entry into cluster analysis for non-comorbid participants (TDC, ADHD, and ASD). Prior to cluster analysis, some variables without strong a priori hypotheses or significant relationships were dropped from the dataset. Feedback-related theta ITPC was collapsed across feedback types due to the lack of interaction between feedback type and diagnosis. ERD values for each hemisphere and trial type were not included, and ERD ratio was collapsed across hemispheres due to the lack of significant relationships. Drift-diffusion model parameters were not included due to the small sample size. Mu and sigma were

removed due to the lack of a priori hypotheses. The complete list of variables can be found in Table 3. Because 24 out of 42 non-comorbid participants were missing data for at least one variable, *k*-means cluster analysis was performed in R using flipCluster, which allows for partial missing data. Rather than traditional implementations where participants are deleted listwise before clusters are formed, then assigned to the closest cluster, this implementation allows for the participants to be included during the initial cluster formation.

To determine the optimal number of clusters, clusters were generated with *k* varied between one and ten, then mean distance to the cluster centroid was calculated at each cluster size to generate an elbow plot. Participants with missing data had missing distance values replaced with the mean of their distance values. Additionally, silhouette plots and mean silhouette scores were generated for each number of clusters to give insight into how well each participant fit into their assigned cluster.

The elbow plot did not provide a clear answer as to the optimal number of clusters. Distance appeared to decrease steadily until six clusters, where it reached a plateau. The mean silhouette score was low (M = .06) and the silhouette plot for the six-cluster solution showed a large degree of misfit, including an entire cluster whose members would better fit into other clusters.

Instead, evaluation of the information contained in the silhouette plots suggested a three-cluster solution (see Fig. 11). Silhouette scores were identical for a two- or three- cluster solution (*M* = .28), but a three-cluster solution explained 10% more of the variance (29%) than a two-cluster solution (19%). Silhouette scores dropped sharply beginning with a four-cluster solution (*M* = .18). Thus, a solution with three clusters was accepted as optimal. After the clusters were established using data from TDC, ADHD, and ASD, participants with a comorbid diagnosis were

assigned to the cluster to which they best fit by finding the cluster with the smallest difference between cluster centroids and the individual's datapoints. Cluster means for each variable can be found in Table 8.

General cluster characteristics

Membership by diagnosis: These clusters did not neatly break down along disorder lines, with all participants clustered according to diagnosis. However, a significant association was found between diagnosis and cluster membership, $X^2(4)> = 10.88$, $p = .03$, such that cluster 1 primarily contained TDC and cluster 2 primarily contained ADHD, while cluster 3 was a mixture of TDC, ADHD, and ASD. Interestingly, while two participants with ASD fit best in cluster 2 and three fit best in cluster 3, none fit best in cluster 1. Cluster membership for COM participants was varied, with two falling into cluster 1, four falling into cluster 2, and two falling into cluster 3. Full details of cluster membership and diagnosis can be found in Table 9 for quick reference; demographic information by cluster can be found in Table 10. Figures 13-19 contain stimulus-related frontal theta and occipitoparietal theta/alpha ITPC; feedback-related frontal theta ITPC, and power in the left and right hemispheres for checks and faces, broken down by cluster.

Full ANOVA results for demographic, clinical, and behavioral comparisons by cluster can be found in Table 11.

Demographics: Prior to the addition of participants with a comorbid diagnosis, clusters were examined for age and IQ differences. Age did not significantly differ across the clusters, nor did nonverbal IQ. After the addition of the COM participants, the clusters still did not differ significantly on age. However, they did significantly differ in terms of nonverbal IQ. Post-hoc tests show that cluster 1 had a significantly higher IQ than cluster 2 (Cluster 1: $M = 110.94$, $SD =$

14.36, range = 77 – 131; Cluster 2: *M* = 96.58, *SD* = 17.05, range = 64 – 139; Cluster 3: *M* = 100.70, *SD* = 19.52, range = 70 – 130).

Clinical characteristics: SCQ scores did not differ between the clusters either before COM participants were added or after.

Accuracy: Accuracy differed across clusters both before and after the addition of COM participants. Follow-up tests indicated that Cluster 2 had significantly lower accuracy than the other clusters, across conditions. There was also a main effect of congruency, with higher accuracy in the congruent condition than the incongruent condition, both before and after the addition of COM participants. There were no interactions between cluster and congruency before or after the addition of COM participants.

Errors of omission: Clusters differed significantly in errors of omission, both before and after COM participants were added/ Follow-up tests indicated that Cluster 2 had more errors than the other clusters. There were no main effects of congruency, either before or after COM participants were added. There were also no interactions between cluster and congruency before or after the addition of COM participants.

Discriminant analysis

The discriminant analysis generated two functions that were linear combinations of the variables used to generate clusters, resulting in two dimensions by which the groups varied. The first, Function 1, accounted for 73% of the ability to discriminate between clusters, while the second, Function 2, accounted for 27%. Variable loadings onto these functions can be found in Table 12 and a scatter plot displaying discriminant scores by cluster and diagnosis can be found in Figure 12.

Function 1 was the primary axis that separated the groups and may represent Stimulus Engagement. The constituent variables that had the strongest positive relationships with this function were stimulus-related frontal theta ITPC and stimulus-related occipitoparietal theta/alpha ITPC. That is, participants with high values of this function generally had reduced cortical variability in response to flanker stimulus presentation, across scalp regions. This was accompanied by lower values of tau, which had a strong negative relationship with this function in both the congruent and incongruent condition. Thus, participants with high values of Stimulus Engagement displayed reduced behavioral variability as indexed by tau, the exponential component of their RT distributions.

Function 2 could potentially be considered as Feedback Responsivity. The variables with the strongest relationships to this function were tied to feedback receipt: feedback-related frontal theta ITPC as well as all four feedback-related occipitoparietal power variables, regardless of sociality or hemisphere. Additionally, this function related positively to tau, particularly in the congruent condition. Thus, participants with high values of Feedback Responsivity showed decreased frontal variability in response to the stimulus onset and increased induced power in occipitoparietal electrodes, accompanied by increased behavioral variability.

Cluster descriptions

Considering functions 1 and 2 together, different phenotypes emerge for each cluster.

Cluster 1: Participants in Cluster 1, which contained 11 TD, 4 ADHD, and 2 comorbid participants, had moderate values for Stimulus Engagement (M = 1.5) and highly negative values for Feedback Responsivity (M = -2.32). During the completion of the task, Cluster 1 had about

average stimulus-related frontal theta ITPC and occipitoparietal theta/alpha ITPC, along with overall decreased frontal ITPC and occipitoparietal power to feedback stimuli.

Cluster 2: Participants in Cluster 2, which contained 4 TDC, 10 ADHD, 2 ASD, and 4 COM, had highly negative values for Stimulus Engagement (M = -3.51) and low values for Feedback Responsivity (M = .55). During the task, Cluster 2 displayed decreased stimulus-related frontal ITPC and occipital theta/alpha ITPC, and mid-range responses to feedback stimuli. This was accompanied by greater behavioral variability, in both the congruent and incongruent conditions.

Cluster 3: Participants in Cluster 3, which contained 5 TDC, 3 ADHD, 3 ASD, and 2 COM, had extremely high values for Function 1 (M = 3.43) but also for Function 2 (M = 2.19). During the task, this cluster had increased frontal and occipitoparietal ITPC to stimulus onset, in addition to increased frontal ITPC and occipitoparietal power in response to feedback stimuli. This relative decrease in cortical variability and increase in responsivity was accompanied by values of tau that generally fell between those of clusters 1 and 2.

Individual clustering of COM

Cluster 1: Two COM participants were clustered into cluster 1, which primarily contained TDC. The first was male, aged 11, with a nonverbal IQ of 120. This participant did not donate complete data; his resting data were unusable due to singing, and his task-related EEG data lacked an adequate number of trials for all variables except stimulus-related frontal theta ITPC and stimulus-related occipitoparietal theta/alpha ITPC. His values for both ITPC measures were moderate, in line with the rest of cluster 1. His behavioral accuracy was high, and his behavioral variability, as estimated by tau, was low, with the expected increase for the

incongruent condition relative to congruent. He made no errors of omission during the first block.

The second was also male, aged 12, with a nonverbal IQ of 124. This participant contributed a complete dataset. Like other members of cluster 1, he had moderate values for stimulus-related ITPC, both frontally and occipitally, and low values for feedback-related frontal theta and occipitoparietal power. His behavioral accuracy was high across conditions and he, too, made no errors of omission. His values of tau were low, and lower for the congruent condition than the incongruent condition.

Cluster 2: Four COM participants best fit into cluster 2, which primarily contained ADHD. The first was female, aged 10, with a nonverbal IQ of 87. This participant had usable data for all except feedback receipt. Her stimulus-related ITPC was low, both in frontal and occipitoparietal sensors, as was typical for cluster 2. Her accuracy was low but above chance, and she had seven errors of omission in each condition during the first block. Her values of tau were high, with only a slight increase for incongruent condition relative to the congruent condition.

The second comorbid participant that fell into cluster 2 was male, aged 8, with a nonverbal IQ of 100. He was able to complete the task but was not compliant with instructions during the rest period, preferring to keep his eyes open. Because he was preoccupied with the keyboard during the task and kept averting his eyes to the keys, his task EEG was unusable. Overall, his accuracy was low; it was above chance in the congruent condition and below chance in the incongruent condition. His values for tau were high across conditions, and substantially higher for the incongruent condition. He made substantial errors of omission (14, congruent; 12, incongruent) and was removed as an outlier before statistical comparisons.

The third comorbid participant in cluster 2 was female, aged 11, with a nonverbal IQ of 85. This participant contributed a complete dataset. She had low stimulus-related ITPC across scalp regions, as well as relatively low feedback-related ITPC and power. Her accuracy was low but above chance in the congruent condition and barely below chance in the incongruent condition. While her tau was high in the congruent condition, it was lower in the incongruent condition. She made 5 errors of omission in the congruent condition and 7 in the incongruent condition.

The fourth comorbid participant sorted into cluster 2 was female, aged 10, with a nonverbal IQ of 64. This participant contributed a complete dataset. She had greater stimulus-related ITPC than her cluster's average across scalp regions, as well as greater feedback-related frontal theta ITPC. Her feedback-related occipitoparietal power was low, however, as was her accuracy. Though she performed above chance in the congruent condition, she performed below chance in the incongruent condition. She had three errors of omission during the congruent condition and 5 during the incongruent.

Cluster 3: The final two comorbid participants fell into cluster 3. The first was male, aged 9, with a nonverbal IQ of 118. He contributed a complete dataset. In line with his cluster, this participant had relatively high frontal theta ITPC after both stimulus onset and feedback onset. Occipitally, he had high power in response to feedback stimuli, particularly in the right hemisphere relative to TDC. His accuracy was near-perfect in the congruent condition but fell to 70% in the incongruent condition. His estimates of tau were low for the congruent condition and higher for the incongruent. He made no errors of omission.

The second comorbid participant in cluster 3 was also male and aged 9. He had a nonverbal IQ of 81, and he, too, contributed a complete dataset. His stimulus-related theta ITPC

was particularly high, though the rest of his stimulus- and feedback-related variables were generally high as well, in line with his cluster. He was nearly 100% accurate, missing only one congruent trial and making 0 errors of omission. His tau parameters were moderate, and nearly identical across conditions.

Discussion

This study sought first to examine several regularities in the literature that have been posited as ways to discriminate between TDC and children with ASD and ADHD**,** both at rest and during the completion of a flanker task. Second, this study aimed to determine whether submitting these regularities to *k*-means cluster analysis would recover distinct disorder-related phenotypes, and whether insight could be gleaned about individual participants with comorbid ADHD+ASD based on their cluster assignment. I will begin by reviewing the individual regularities separately for resting EEG, task-related EEG, and behavior, then consider the cluster analysis.

Resting EEG

Hypotheses for the resting data included increased frontal TBR and rightward AS in ADHD, as well as increased central high beta/low gamma in ASD. Contrary to expectations, significant group differences were not found for any of the resting variables. It is possible that our short resting segment (3 m, 2 m of which were eyes-open) was not long enough to capture a stable measure of brain activity at rest, though group differences have been found with short segments (DiStefano, Dickinson, Baker, & Jeste, 2019).

Regarding TBR, the lack of significant results was not entirely unexpected. Previous research has found null results when utilizing a theta band that was based on the individual

participant's peak alpha frequency, even when significant results were found using a standard theta band (Lansbergen et al., 2011). It is possible that participants with ADHD have a lower alpha band than TDC, though there were no significant differences found between peak alpha frequency in our sample. Similar mechanisms may be at play regarding AS, where we also used individualized alpha bands and failed to find significant effects, though ours would not be the first null result found in the literature (Alperin, Smith, Gustafsson, Figuracion, & Karalunas, 2019; Gordon et al., 2010). Recent research suggests that rightward AS, which is considered a measure of approach motivation, may only differ from TDC in children with low negative affect (Alperin et al., 2019), which may have contributed to our lack of significant results.

In terms of resting central high beta/low gamma in ASD, hypotheses did not bear out: there were no significant differences between groups. This may be driven in part due to our small sample of ASD participants; though we aimed to recruit 20, we were unable to fill this group due to a high incidence of medication use, such as anti-depressants or anti-psychotics, that would be unethical or unsafe to request temporary stoppage and extended washout for the purposes of research, in contrast to stimulants commonly used to treat ADHD, which have a short washout period and few risks associated with temporary stoppage. Thus, more than half of the ASD participants in this statistical comparison had comorbid ADHD+ASD, and their phenotypes may differ at the level of the individual.

At the same time, it is possible that the age range used in this study was not ideal to detect changes in gamma power, which is expected to undergo maturational changes as participants approach adolescence. For example, previous studies have found significantly less beta and gamma power in infants with ASD than TDC but no difference in toddlers (Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). In our own lab, we have found

no difference in high beta/low gamma power in pre-adolescent children, but significantly more in adolescents with ASD than TDC (De Stefano et al., 2019). The age range used in the present study may reflect a transitional period, complicated further by individual differences in disorder severity and thus differing rates of maturation.

Task-related EEG

During the task, it was hypothesized that ADHD would have decreased frontal theta ITPC in response to both the flanker stimulus and the feedback stimuli, as well as increased pre-feedback frontal AS. It was expected that participants with ASD would have decreased early sensory phase-locking to the flanker stimulus, as measured by stimulus-related theta/alpha occipitoparietal ITPC. It was also expected that ASD would display decreased frontal theta ITPC in response to the feedback stimuli, and decreased ratio of power for faces relative to checks, as measured by ERS ratio.

Overall, these predictions did not bear out. Participants with ADHD had marginally less frontal theta ITPC to the flanker stimulus, which fit the direction of our hypothesis but did not attain statistical significance. They also did not display decreased theta ITPC to the feedback stimuli, nor did they have increased rightward AS during feedback anticipation, despite the expectation that feedback anticipation may elicit group differences in motivational style and thus have effects on AS. Feedback-related theta waves have been characterized as signaling the need for cognitive control, particularly in response to negative feedback (Cavanagh & Frank, 2014). Because we were only able to analyze positive feedback due to low trial counts for negative feedback, it is possible that we were unable to characterize differences in frontal theta ITPC that would have emerged in the negative feedback condition. Alternatively, it is possible that due to the deterministic nature of our feedback, proper attention and error monitoring during the

response stage reduced the value of feedback to TDC and eliminated group differences. Similar mechanisms may be at play with rightward AS. It is also possible that the pictures used to provide feedback were not inherently rewarding enough to elicit motivational differences. This is consistent with the literature, which found significant differences between ADHD and TDC when a monetary reward was associated with positive feedback (van Meel et al., 2011) but not when participants were given feedback without an associated reward or punishment (Groen et al., 2008; van Meel et al., 2011).

Considering constructs related to ASD during the task, there were no differences between groups for occipitoparietal theta/alpha ITPC to the flanker stimulus; participants with ASD displayed the same phase-locking to the flanker stimulus as those without a diagnosis. Given our small sample size and the expected heterogeneity of participants (both ASD-only and comorbid ADHD+ASD), it is possible that we were simply underpowered to detect group differences.

Contrary to predictions, participants with ASD displayed increased frontal theta ITPC in response to feedback. This result is inconsistent with the literature, which has previously found decreased ITPC (thus increased neural variability) in ASD (van Noordt et al., 2017). It is possible that because we required our participants to be free of psychotropic medications and have at least a verbal or nonverbal IQ of 70, our sample may not reflect the entire range of differences found in ASD.

At the same time, participants with ASD had no significant difference in occipitoparietal theta/alpha power in response to feedback, either examined alone or in a ratio of power for faces/checks. We did, however, find significantly increased left hemisphere power in ASD relative to other groups. While the four participants in this comparison with an ASD-only diagnosis had on average greater ERS in the left hemisphere than the right, on average, the COM

participants included appeared to have greater power in the right hemisphere. Overall, this appears as an ASD effect of reduced differentiation between the hemispheres. This, at least, is consistent with the literature, which suggests that reduced hemispheric lateralization to visual stimuli as an early marker of ASD (Keehn, Vogel-Farley, Tager-Flusberg, & Nelson, 2015).

Across diagnostic groups and hemispheres, our sample displayed increased ERS to nonsocial relative to social stimuli. That is, they had more induced power in response to checks than they did to faces, counter to the typical expectation of increased power for faces relative to objects (Rousselet et al., 2007). Though care was taken to equate the visual input by scrambling the face stimulus to generate the check, it is hard to equate the feedback content between a face and a check mark. It is possible that evaluation of the time course of the waveform might help understand whether stimulus properties caused this discrepancy.

In terms of ratios of faces to checks, ADHD displayed significantly reduced bilateral ERS ratios and marginally reduced ERD ratios. That is, they had greater early occipitoparietal theta/alpha power increases to checks relative to faces, and marginally greater later occipitoparietal theta/alpha power decreases to checks relative to faces. While social deficits have been found in ADHD, they are generally explained as a consequence of typical ADHD symptoms such as inattention that have a negative impact on social development (Leitner, 2014). The current result suggests that these deficits may be evident in early sensory components captured over sensory cortex.

Behavior

Overall, there were no group differences in accuracy, but participants with ADHD were more likely to make errors of omission. Additionally, when decomposing reaction time distributions into mu, sigma, and tau, ADHD displayed significantly increased tau parameters

but not mu or sigma. While mu and sigma describe the normally distributed RTs, tau describes the longer RTs contained in the right tail of the distribution and acts as an estimate of RTV. Our results are consistent with reports of RTV in ADHD that only find significant differences in tau, but not mu or sigma (Kofler et al., 2013). Taken together, these results support a characterization of ADHD as displaying lapses in attention that either lead to errors of omission or longer than typical RTs.

Comparison of drift-diffusion model parameters found generally null results. Drift rate, or *v,* was significantly larger for the congruent condition than incongruent, while T_{er}, non-decision time, was significantly larger for the incongruent condition. The speed-accuracy tradeoff parameter, *a,* did not differ. These findings are consistent with task difficulty effects. In the congruent condition, less conflicting information should lead to less noise in the decision process and faster overall drift rates. In the incongruent condition, the need to encode and extract relevant information should increase, thus increasing non-decision time. There were no effects of diagnosis for any of the parameters, which may be due to our limited sample that contributed data usable by this model. Future studies may emphasize attaining more trials and potentially utilizing the full drift-diffusion model. Because this model allows across-trial variability, it may be more suited to recover group differences such as those found in the literature (Karalunas et al., 2012; Metin et al., 2013; Salum et al., 2014)

Cluster analysis

Though many of our comparisons failed to attain significance when examined across diagnostic lines, submission to *k*-means cluster analysis brought interesting patterns to light. Cluster analysis returned three clusters, as hypothesized, that contained primarily participants

from each diagnostic group. Cluster 1 contained primarily TDC, while Cluster 2 contained primarily ADHD. Cluster 3 had the largest subset of ASD-only participants, with three, while the other two ASD-only participants fell into Cluster 2. Cluster 3 also contained a mixture of TDC and ADHD.

The first cluster had high accuracy and few errors of omission. Their medium-range ITPC in response to the flanker stimulus, both frontally and occipitally, was accompanied by low neural consistency and responsivity to feedback stimuli, as measured by feedback-related frontal theta and occipitoparietal power. Given that this cluster is made up mostly of participants without a clinical diagnosis, this suggests that "typical" performance may be reflected in moderate consideration of the stimulus during onset. Because feedback was deterministic, appropriate processing during stimulus onset and response may have negated the need for extended processing of the feedback stimulus. Participants in this cluster also evidenced decreased behavioral variability, particularly in the congruent condition, as compared to the other clusters. The two COM participants sorted into this cluster both had high nonverbal IQs and committed few errors of omission. Taken together, this suggests a balanced phenotype that performed the task adequately and efficiently.

Cluster 2, on the other hand, had decreased frontal and occipitoparietal ITPC in response to the flanker stimulus, accompanied by moderate responses to the feedback stimuli. Unlike the other clusters, behavioral performance was poor, with decreased accuracy, increased errors of omission, and the highest behavioral variability. Of the four COM participants sorted into this cluster, only two were able to yield complete datasets, and all four exhibited errors of omission.

Participants in this cluster were primarily diagnosed with ADHD, which suggests that these measures may reflect an inability to sustain attention to what was intended to be a boring

task. All three of the female COM participants in the study fit best into this cluster, which may not be surprising. Research suggests that girls must display more severe symptoms than boys before parents consider their behaviors worrisome (Mowlem, Agnew-Blais, Taylor, & Asherson, 2019). Because this cluster was the only one that was impaired in completing the task, it follows that participants with the greatest impairment would fall here. Notably, four TDC also fit best into this cluster. While ADHD is diagnosed based on behavioral observation, there is no discrete cutoff that separates children with the disorder from those without. Rather, diagnosis requires a judgment that symptoms of inattentiveness and/or hyperactivity interfere significantly with day-to-day life. TDC who were unable or unwilling to adequately perform the task may only show impairment in the context of our research study, which would support their lack of clinical diagnosis.

One commonly suggested mechanism for ADHD (Sagvolden et al., 2005; Sonuga-Barke, 2005) that may underlie these results is hypodopaminergic neurotransmission. As previously mentioned, one of the most common treatments for ADHD is methylphenidate, which blocks the reuptake of dopamine by DAT1 at the synaptic cleft. This increases the availability of dopamine in the ventral striatum, as well as in prefrontal and temporal regions, with the amount of change related to the amount of change in inattentive symptoms (Volkow et al., 2012). There is evidence to suggest that children diagnosed with ADHD who have 10/10 homozygous DAT1 alleles, which code for increased DAT1 expression, have impaired performance tests of sustained attention and increased RTV relative to diagnosed children with one or none of these alleles (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Loo et al., 2003). Additionally, the administration of methylphenidate was shown to modulate EEG activity in opposite directions based on whether a participant had homozygous 10/10 alleles (Loo et al., 2003), suggesting that

children with high RTV and poor sustained attention may be impacted differently by the use of stimulants.

Frontal theta ITPC, which was decreased in this cluster in response to stimulus onset, may reflect coordination between dopaminergic regions within the basal ganglia and the medial prefrontal cortex (Cavanagh & Frank, 2014). Variability in frontal theta phase during stimulus presentation has been found to correlate with RTV not only in participants with ADHD (McLoughlin et al., 2014) but also in TDC throughout the lifespan (Papenberg, Hammerer, Muller, Lindenberger, & Li, 2013). Aberrant RTV found in ADHD has been shown to be improved by treatment with methylphenidate (Groom et al., 2010; Kofler et al., 2013), but not by nonstimulant treatments (Kofler et al., 2013). Taken together, this suggests that participants in Cluster 2 may benefit the most from the use of traditional ADHD treatments such as methylphenidate, which augment dopamine activity.

Our third cluster contained participants from all diagnostic groups. While clusters 1 and 2 displayed about average neural activity in response to either the flanker (cluster 1) or the feedback stimuli (cluster 2), this cluster displayed above-average activity to both, across all measures. This was accompanied by low behavioral variability. This cluster may represent a phenotype with increased sensory responsivity and/or increased task engagement relative to the other clusters. However, it does not appear that this potential increased task engagement was necessary to complete the task: compared directly to cluster 1, this cluster displays more ITPC to the flanker, and ITPC and power to the feedback stimuli, but no increase in behavioral performance.

Cluster 3 does not represent a single diagnosis, complicating its interpretation. However, it contained 4 participants with pure ADHD diagnosis. While ADHD is typically considered in

terms of inattentiveness, researchers have emphasized the importance of attentional control in general (Hinshaw, 2018). This view suggests that ADHD symptoms may result from inability to regulate attentional demands by either increasing or decreasing attention as the task requires. Other researchers have suggested a specifically "overfocused" subtype within ADHD, with a hypothesized etiology of increased norepinephrinergic and dopaminergic neurotransmission that leads to perseveration and selective attention (Kinsbourne, 1991).

Though limited in number, Cluster 3 also contained the largest subset of ASD-only participants. Previous studies of children with ASD have suggested there is considerable variability in their sensory experience, with some appearing to show sensory hyposensitivity and others displaying hypersensitivity (DeBoth & Reynolds, 2017; Schauder & Bennetto, 2016). One study investigating sensory responses in children with ASD using fMRI found that the magnitude of response to visual stimuli in many brain regions, including primary sensory cortices, correlated significantly with parent reports of sensory sensitivity, suggesting that exaggerated early sensory responses may underlie complaints of hypersensitivity (Green et al., 2013). Another study used EEG to examine visual processing in ASD, which allows for a greater understanding of the time course of group differences. Baruth, Casanova, Sears, and Sokhadze (2010) found that participants with ASD had larger and earlier P1 amplitudes to non-target stimuli on a go/no-go task than typically developing participants, as well as increased P2 amplitudes to target stimuli. Together, this suggests that increased reactivity in these participants may begin relatively early in primary visual cortex.

The concept of overfocus has also been applied to ASD. Another study used cluster analysis to understand symptom reports from children with ASD, including parent responses to a survey intended to gauge overfocus (Liss et al., 2006). They found that nearly a third of their

sample fell into clusters that were either very or mildly over-focused, and that symptom reports of improper allocation of attention correlated with those of sensory over-reactivity. This provides evidence that, at least in the context of ASD, increased sensory responsivity may relate to attentional difficulties. Unfortunately, the clinical scales used to characterize our study participants did not include a measure specifically designed to capture attentional overfocus, so clinical/behavioral sequelae of the over-focused neural phenotype cannot be confirmed in the current sample.

The biological underpinning of this cluster's pattern of results is hard to characterize, but altogether, it is possible that Cluster 3 represents a cohort of children with increased early sensory sensitivity. Increased early sensitivity has been found in ASD, and is usually considered an effect of a dysregulation of cortical excitation and inhibition (Rubenstein & Merzenich, 2003). Like much of the cortex, primary visual areas are comprised of mini-columns of GABAergic interneurons and glutamatergic pyramidal cells(Rockland & Ichinohe, 2004). Stimulation of GABAergic neurons in visual cortex has been shown to decrease firing rates of glutamatergic neurons, sharpening visual representations in rats (S. H. Lee et al., 2012). Greater GABA content has also been related to decreased BOLD response in humans (Donahue, Near, Blicher, & Jezzard, 2010), suggesting that larger visual responses to feedback stimuli in this cluster could potentially represent reduced inhibition in visual cortex.

It is noteworthy that alterations of the ratio of excitation/inhibition in ASD are generally related to *increased* neural variability and thus lower ITPC (Edgar et al., 2016), which is not the pattern seen here. It is possible that other mechanisms may also lead to this pattern of results. Pharmacological augmentation of dopamine has been related to increased occipital blood flow and increased signal-to-noise ratio in response to visual stimulation in rhesus monkeys (Zaldivar,

Rauch, Whittingstall, Logothetis, & Goense, 2014). Application of dopamine directly to visual cortex did not produce the same effects (Zaldivar et al., 2014), suggesting that the changes seen in visual cortex result from top-down mechanisms generated elsewhere. Increased dopamine activity could also have effects on frontal theta, where power in response to errors has been found to depend on the integrity of white matter tracts between the medial frontal cortex and the ventral striatum (Cohen, 2011). These theta oscillations have been suggested as one possible way by which attention could modulate sensory signals (Cavanagh & Frank, 2014). Together, a phenotype with increased dopaminergic neurotransmission may present as having highly consistent frontal theta activity that contributes to the decreased signal-to-noise ratio and increased power found over occipital electrodes. Behaviorally, this may present as overly focused on the task at hand and only to be negative when task disengagement must occur.

In addition to these participants with ADHD and ASD, two COM participants were sorted into Cluster 3. Both contributed complete datasets with high accuracy and few errors of omission. True to their cluster, these participants displayed robust responses to both the flanker and feedback stimuli. Given the disparities in both brain activity and behavior, it is questionable whether treatments that would help participants in Cluster 2 would also apply to Cluster 3. While symptoms of inattention may be expected to be decreased by stimulants such as methylphenidate, there is less evidence that symptoms of increased focus can be altered this way. Few studies have been completed with this end point, but one examination of symptom profiles compared typically developing adults to those with ADHD who were or were not taking methylphenidate. The researchers found that both ADHD groups had significantly more symptoms of increased focus than participants without an ADHD diagnosis (Ozel-Kizil et al.,

2016). Perhaps more importantly, they found that the groups did not differ from each other, suggesting that methylphenidate may not effectively control these symptoms.

It is also important to note that Cluster 3 contained five participants who do not have a clinical diagnosis. While overfocus or "hyperfocus" is typically considered in terms of clinical populations, the general psychology literature describes a state termed "flow" that is described similarly (Ashinoff & Abu-Akel, 2019). It is possible that the distinction between a clinical diagnosis and a TDC displaying the behavior may lie in attentional control: a TDC may have the ability to engage and disengage from this state at will, while a clinical diagnosis may be given to children who display difficulty controlling this behavior. Future work should consider utilizing an approach that can disentangle voluntary, tactical engagement in this state from involuntary, deleterious engagement that may be driven by a clinical disorder.

Limitations

This study was not without its limitations. We were unable to recruit enough participants to fill the entire ASD and COM groups, likely due to our medication exclusion criteria. This left us unable to make firm conclusions about the measures that were expected to relate primarily to ASD. Regarding task performance, many participants had extremely high accuracy. This complicated any analysis of positive vs. negative feedback and made it hard to determine whether the increased ITPC and power utilized by Cluster 3 would confer an advantage or disadvantage if appropriately taxed. Future studies may examine this by increasing task difficulty, potentially by reducing the stimulus duration.

Finally, our pattern of missing data was such that participants in Cluster 2 tended to be missing feedback-related variables. Given the lower accuracy found in this cluster, it follows that there would be fewer positive feedback trials available for analysis. Despite this, behavioral and

stimulus-related EEG measures were able to separate this cluster from the others. Future studies may emphasize an increase in trial numbers to ensure that even poor performers are able to donate complete data.

Conclusion

ADHD and ASD are both highly heterogeneous disorders, with symptom overlap and differing developmental trajectories that provide a challenge for the clinician to diagnose and for the researcher to study. Few regularities in the ADHD/ASD literature replicated in our study. However, application of cluster analysis led to three clusters with differing phenotypes. One cluster, containing primarily ADHD, was marked by behavioral and neural variability. This cluster may represent the typical hypodopaminergic portrayal of ADHD, and participants in this cluster may thus respond favorably to use of stimulants. Another, containing representatives from all diagnostic groups, including most participants with ASD, was marked by robust occipitoparietal responses to feedback and neural *in*variability. This cluster may represent a differing failure of cognitive control caused by hyperdomanergic circuits, thus may respond less favorably to the use of stimulants that increase dopamine activity. As expected, children with a comorbid ADHD+ASD diagnosis differed individually in the cluster to which they best fit. Similarly, they likely differ in the most effective treatment, underscoring the importance of a holistic view of their behavior but also their brain activity.

Acknowledgements

Thank you to my advisors, Drs. Lauren Ethridge and Michael Wenger, for helping me learn everything I know. Their endless patience and expert guidance have left a mark that will never be erased. I would also like to thank Drs. Scott Gronlund, Hairong Song, and Han Yuan for serving on my committee. Their feedback has improved this work immensely.

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More personally, thank you to my parents, Ann & John De Stefano, and my siblings, David, Tommy, and Emmy, for loving me, raising me, and always cheering for me. Mom, I wish you could be here to see this.

Finally, thank you to my partner, Ryan McAdoo, and our daughter, Daniela, for holding down the fort and keeping me anchored. I would not have entered graduate school without Daniela as a motivation, and I would not have stayed the path without Ryan by my side. Ryan & Daniela, thank you. I love you both more than words.

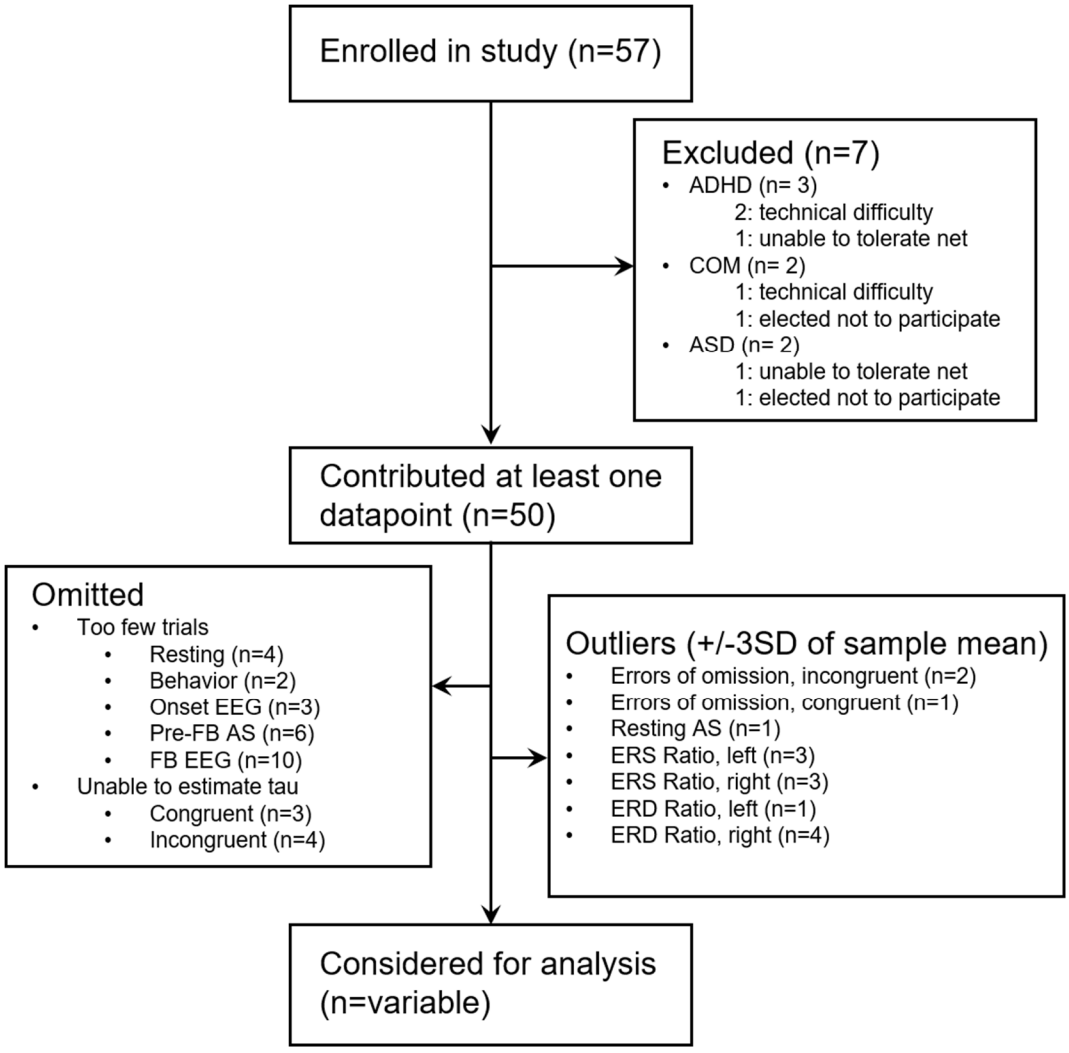

Figure 1. Consort diagram including reasons for exclusion during collection and number excluded for each variable or set of variables thereafter.

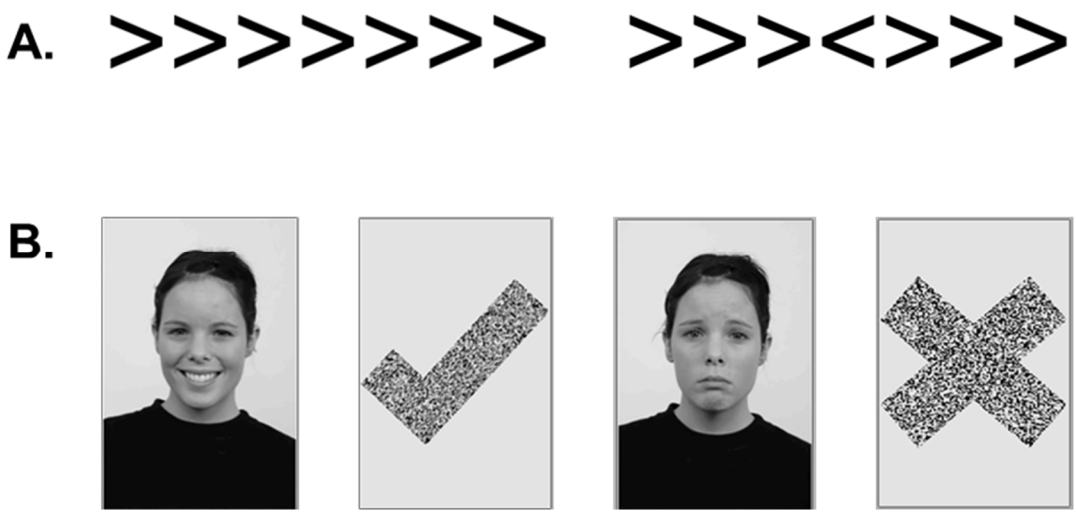

Figure 2. A) Example stimulus arrays, congruent (left) and incongruent (right). B) Possible feedback stimuli: social-positive, happy face; nonsocial-positive, check; social-negative, sad face; nonsocial-negative, check.

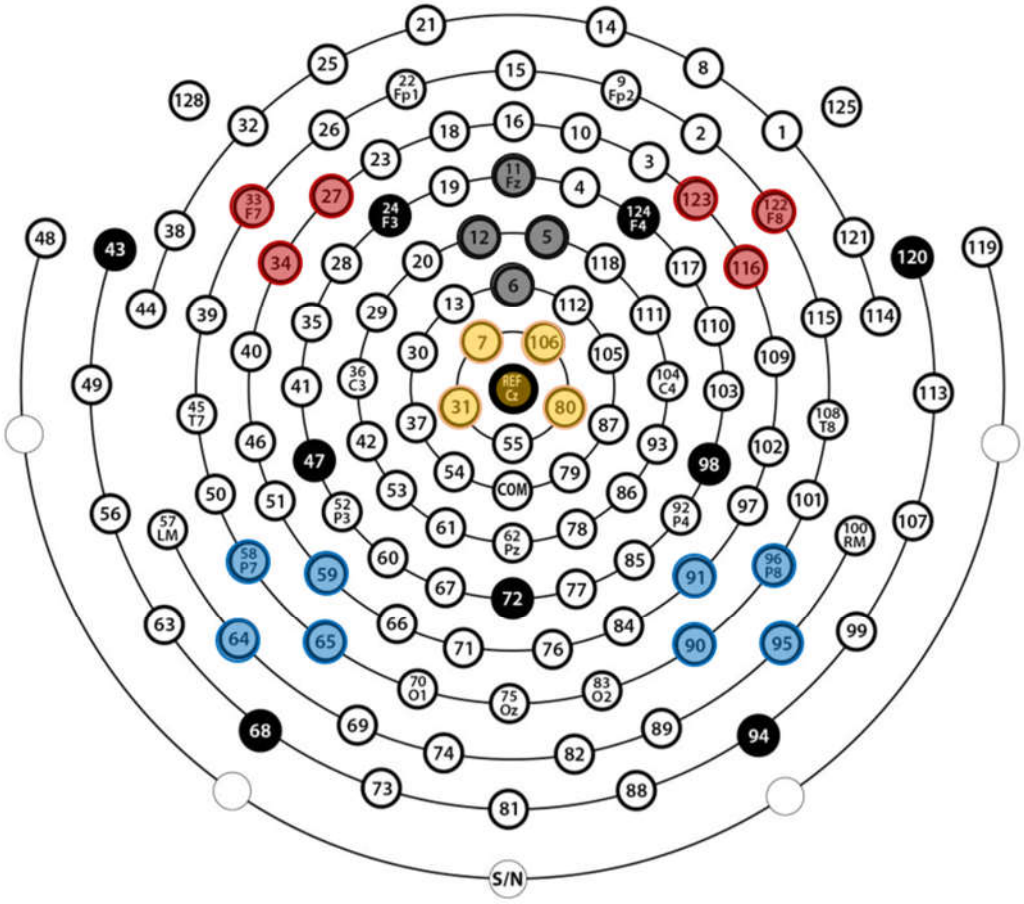

Figure 3. EGI HCGSN electrode map with electrodes for each comparison highlighted. Red, lateral frontal electrodes used for resting and feedback anticipation-related alpha asymmetry. Gray, frontal electrodes used for stimulus-related and feedback-related theta ITPC. Orange, central electrodes used for resting gamma. Circled in black, Cz, used for estimation of resting TBR. Blue, occipitoparietal electrodes used for stimulus-related and feedback-related theta/alpha ITPC.

Figures

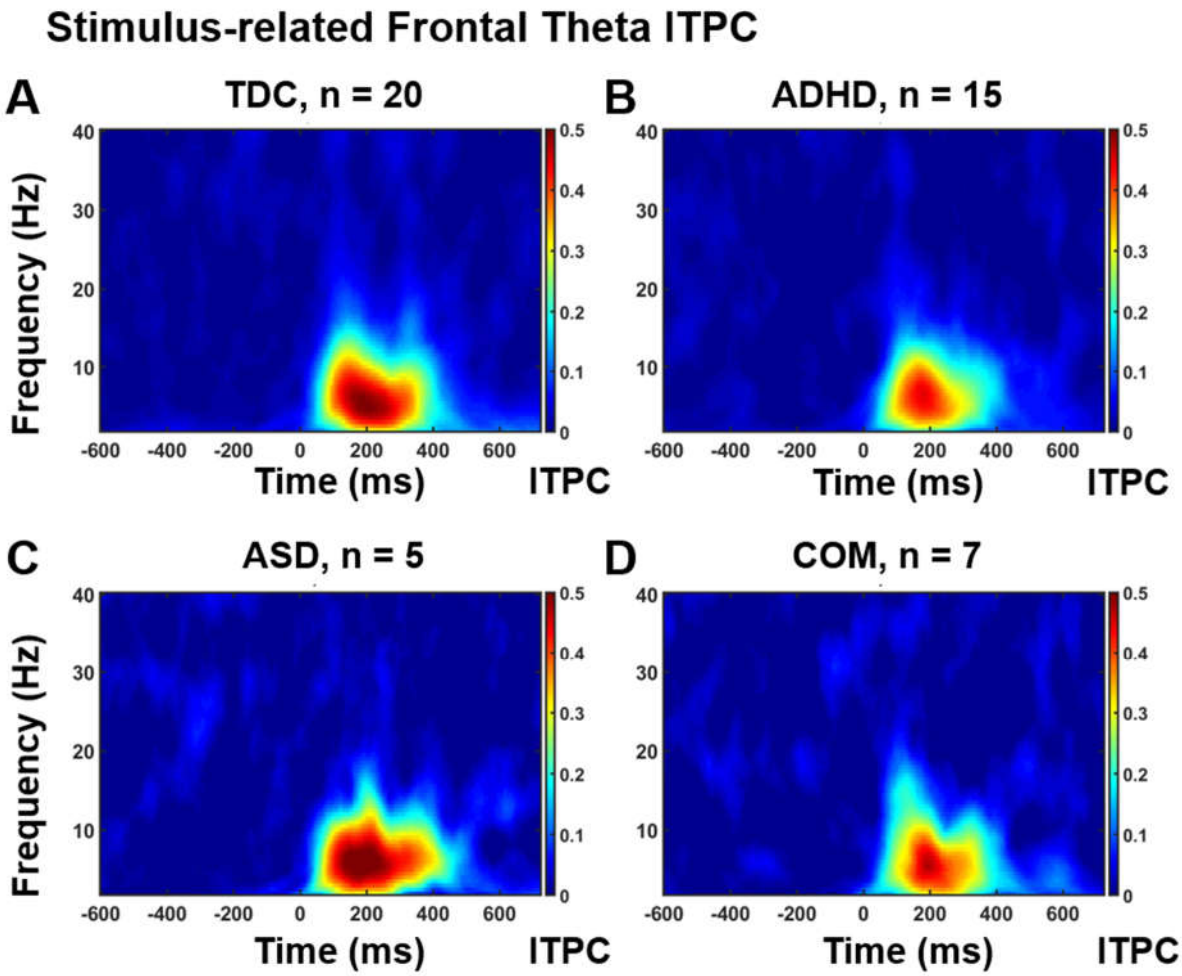

Figure 4. Stimulus-related frontal theta ITPC in A) TDC, B) ADHD, C) ASD, and D) COM participants.

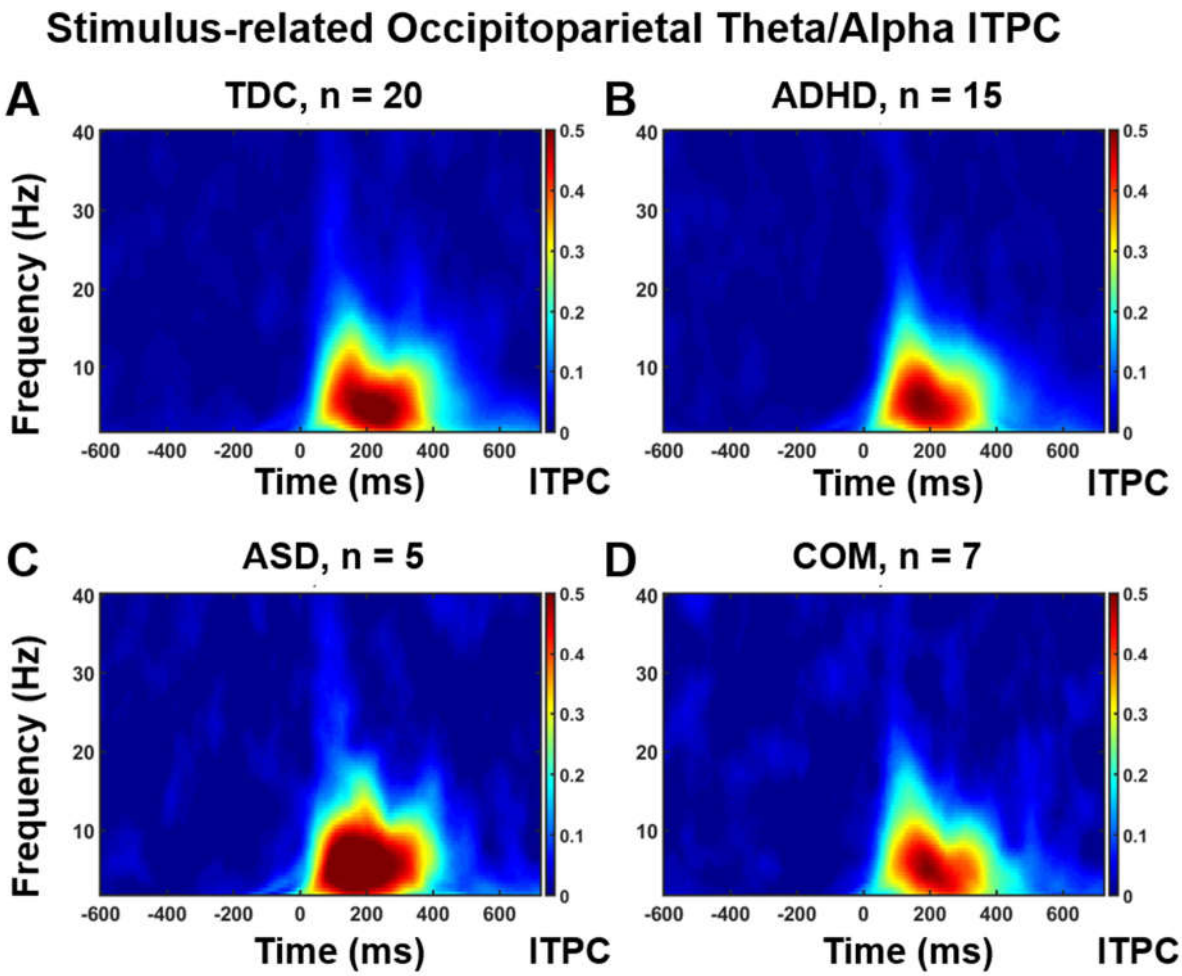

Figure 5. Stimulus-related occipitoparietal theta/alpha ITPC in A) TDC, B) ADHD, C) ASD, and D) COM participants.

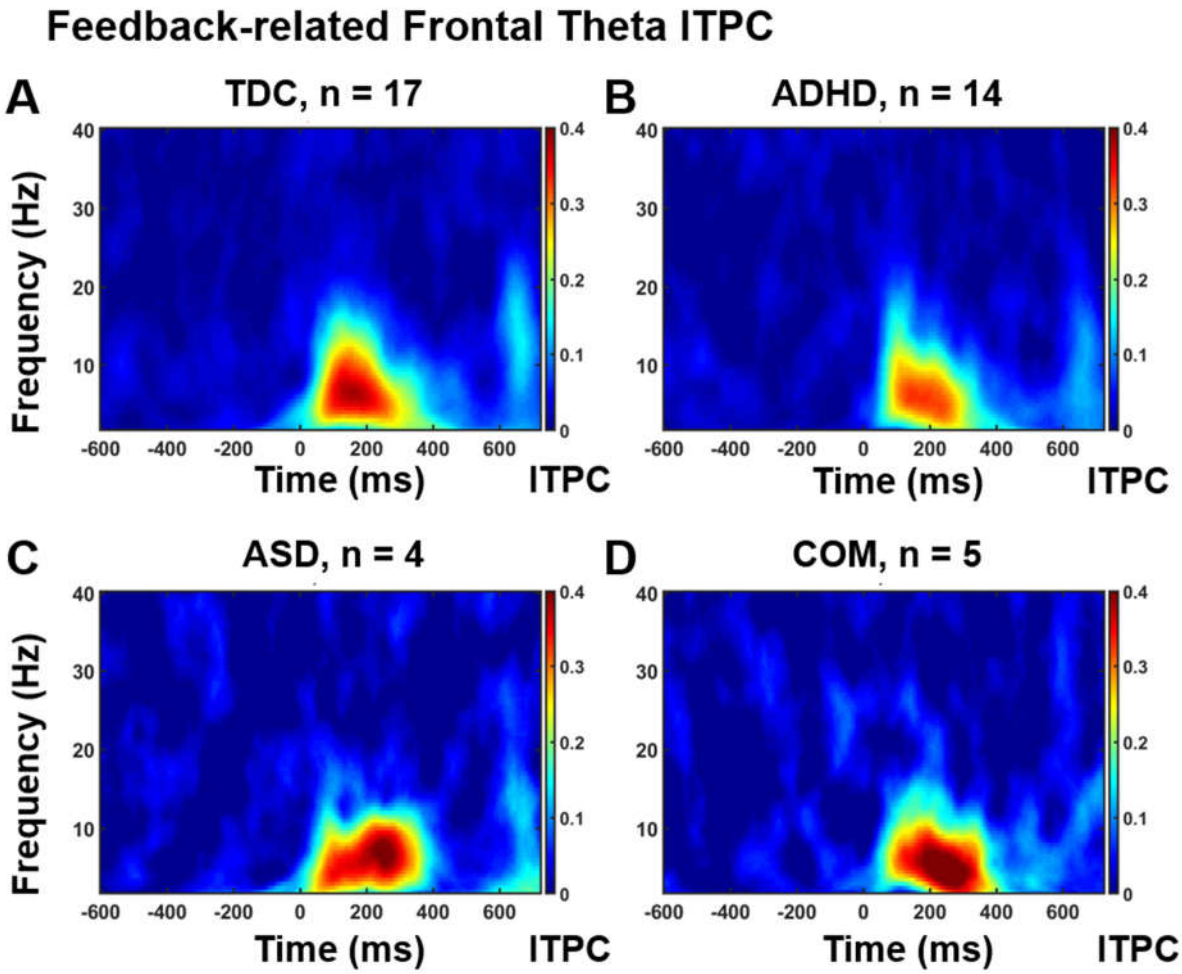

Figure 6. Feedback-related frontal theta ITPC in A) TDC, B) ADHD, C) ASD, and D) COM participants.

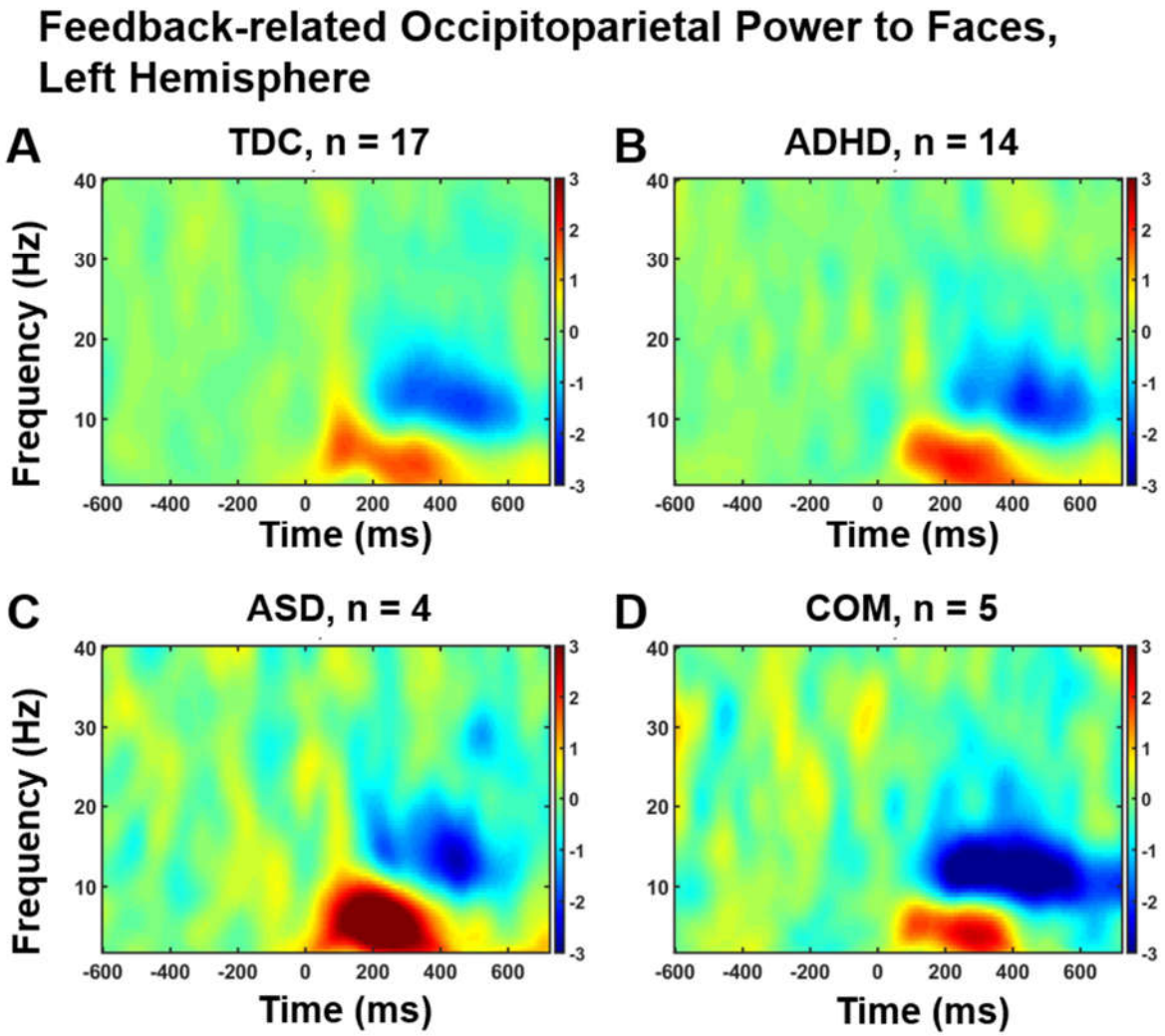

Figure 7. Feedback-related occipitoparietal theta/alpha power in response to faces in the left hemisphere in A) TDC, B) ADHD, C) ASD, and D) COM participants.

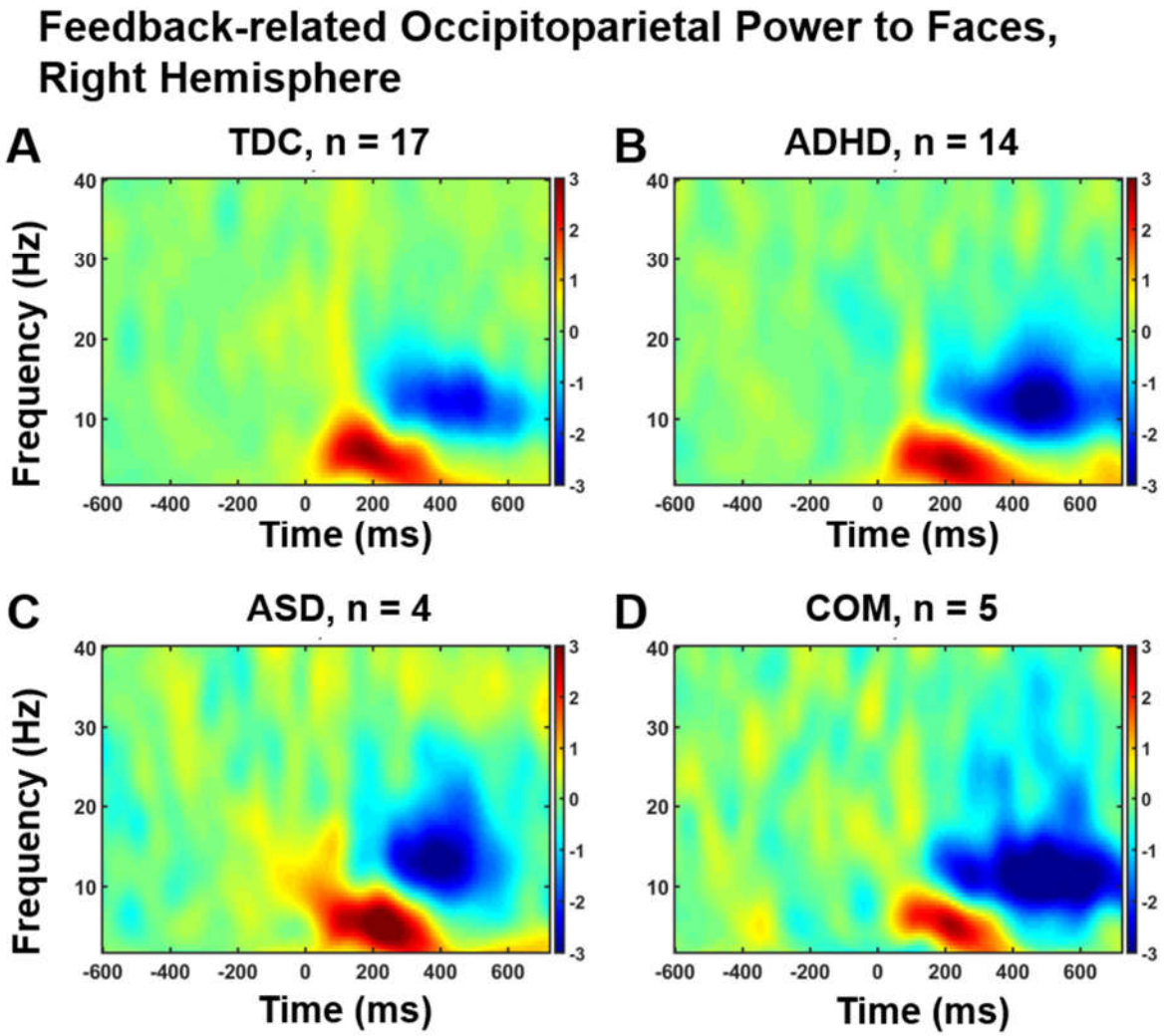

Figure 8. Feedback-related occipitoparietal theta/alpha power in response to faces in the right hemisphere in A) TDC, B) ADHD, C) ASD, and D) COM participants.

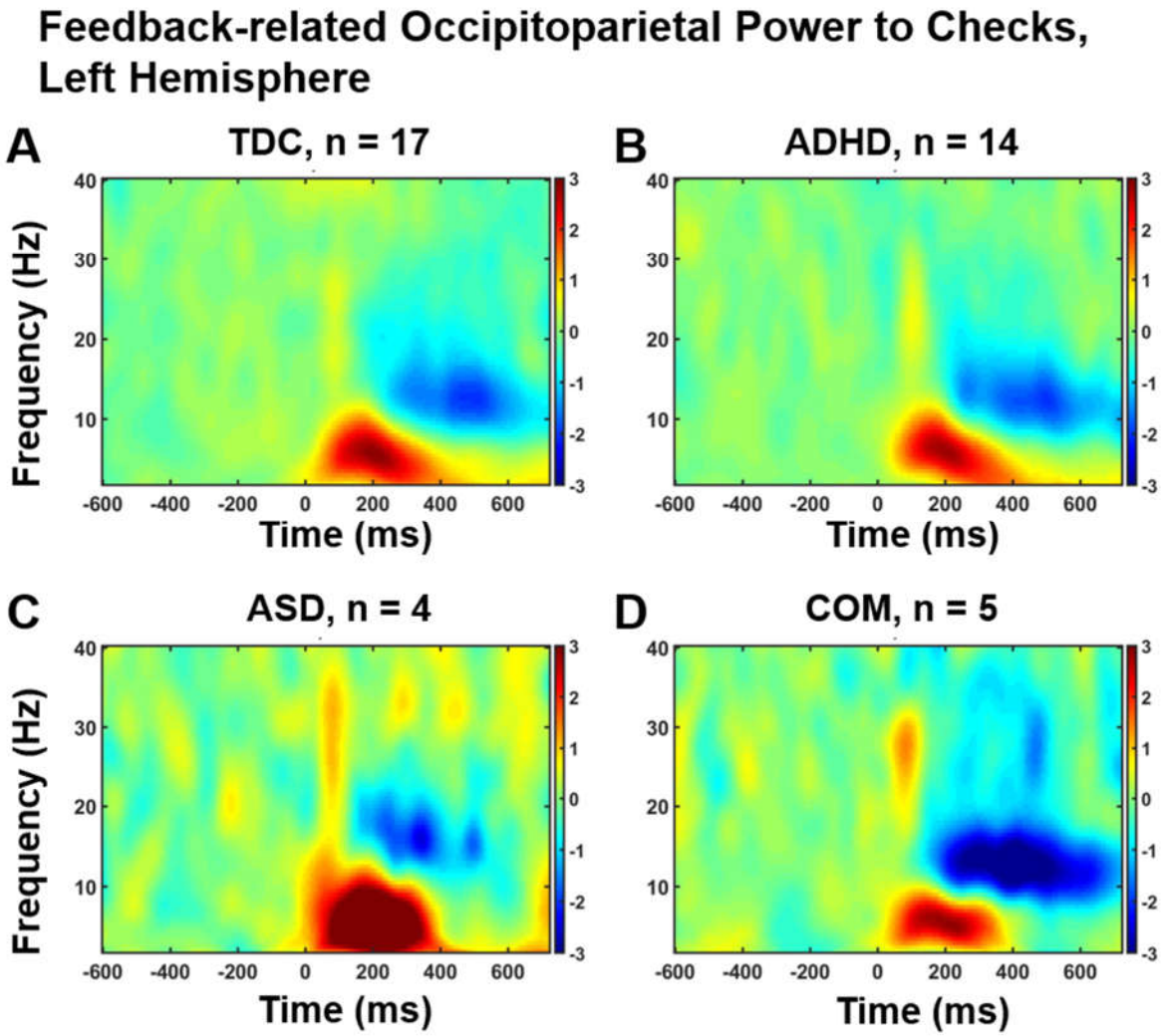

Figure 9. Feedback-related occipitoparietal theta/alpha power in response to checks in the left hemisphere in A) TDC, B) ADHD, C) ASD, and D) COM participants.

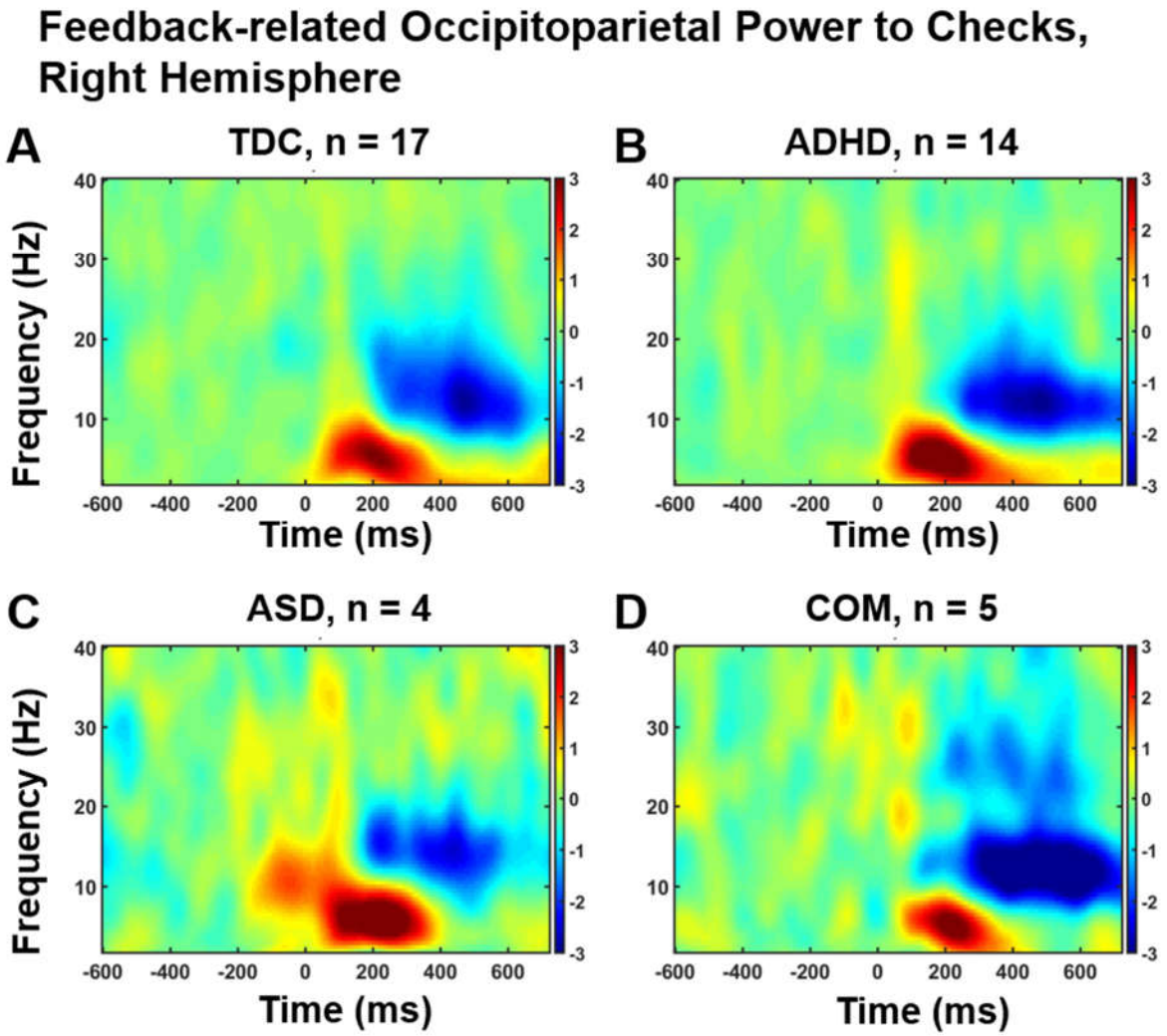

Figure 10. Feedback-related occipitoparietal theta/alpha power in response to checks in the right hemisphere in A) TDC, B) ADHD, C) ASD, and D) COM participants.

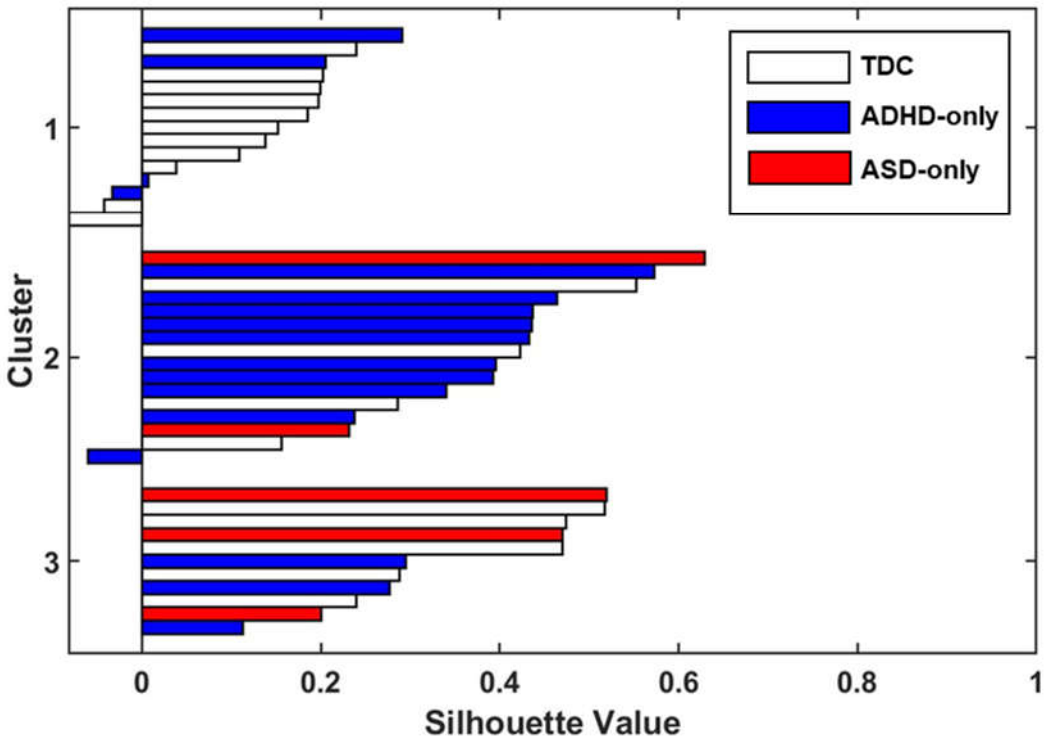

Figure 11. Silhouette plot for 3-cluster solution, color coded by diagnostic group. TDC = white; ADHD = blue; ASD = red.

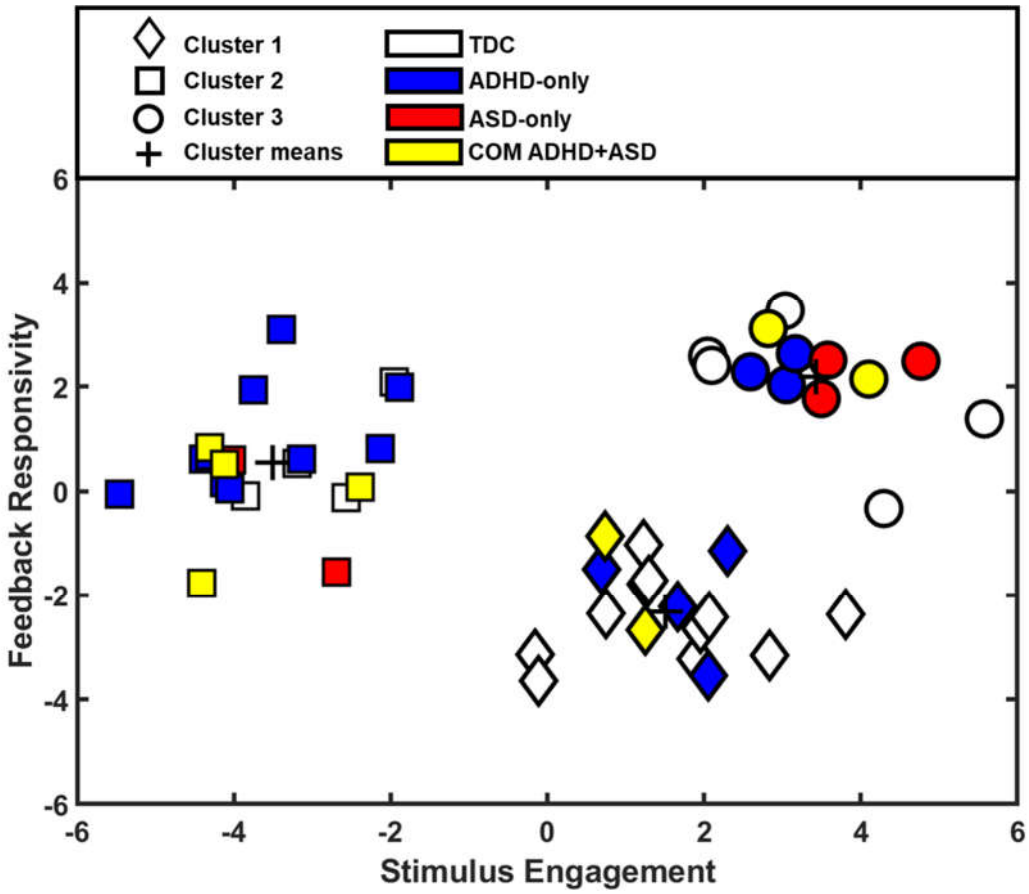

Figure 12. Scatter plot displaying scores on discriminant functions by cluster membership (shape) and diagnosis (color). Cluster 1 = diamonds; Cluster 2 = squares; Cluster 3 = circles. TDC = white; ADHD = blue; ASD = red; COM = yellow.

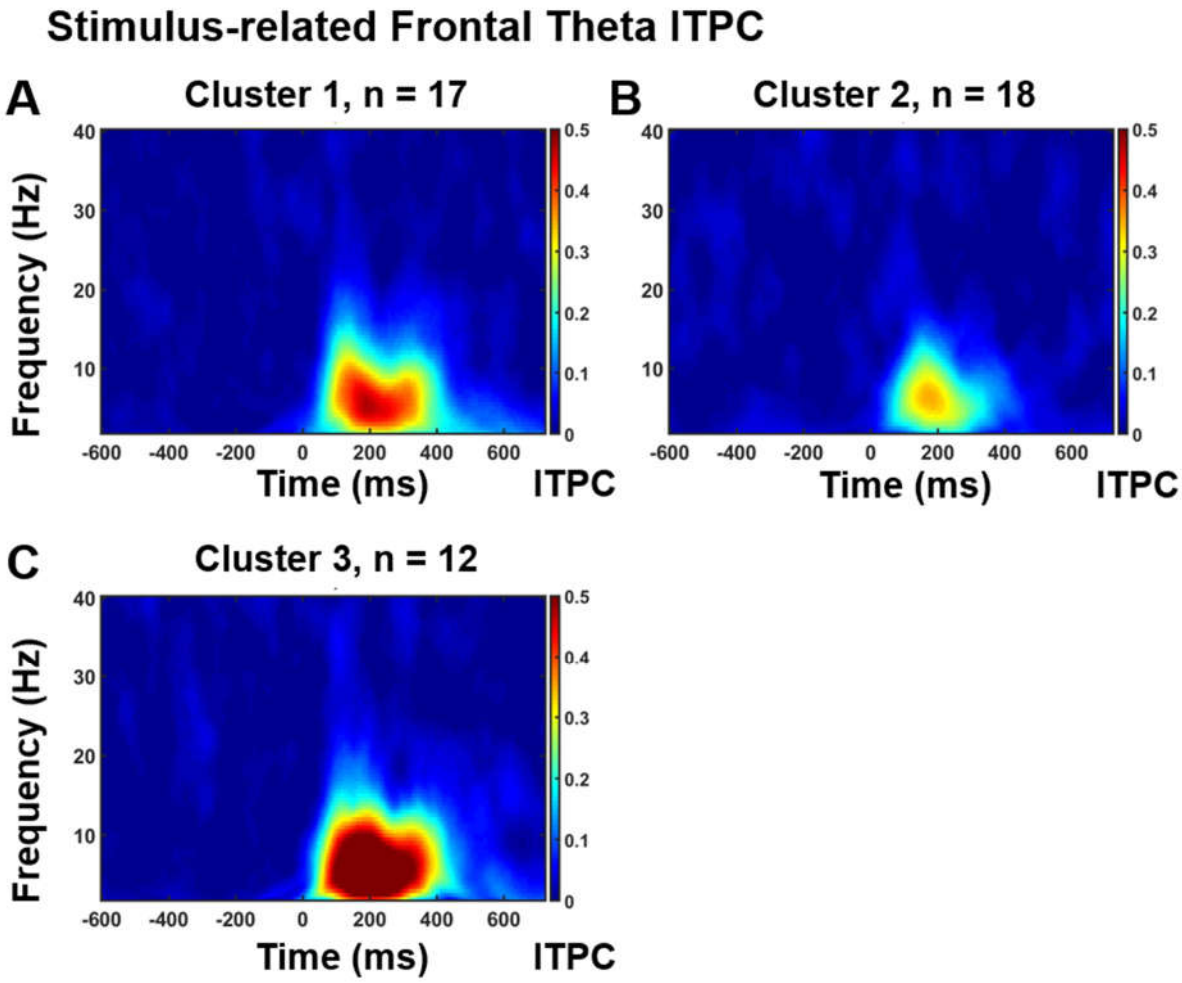

Figure 13. Stimulus-related frontal theta ITPC in participants that best fit into A) Cluster 1, B) Cluster 2, C) Cluster 3.

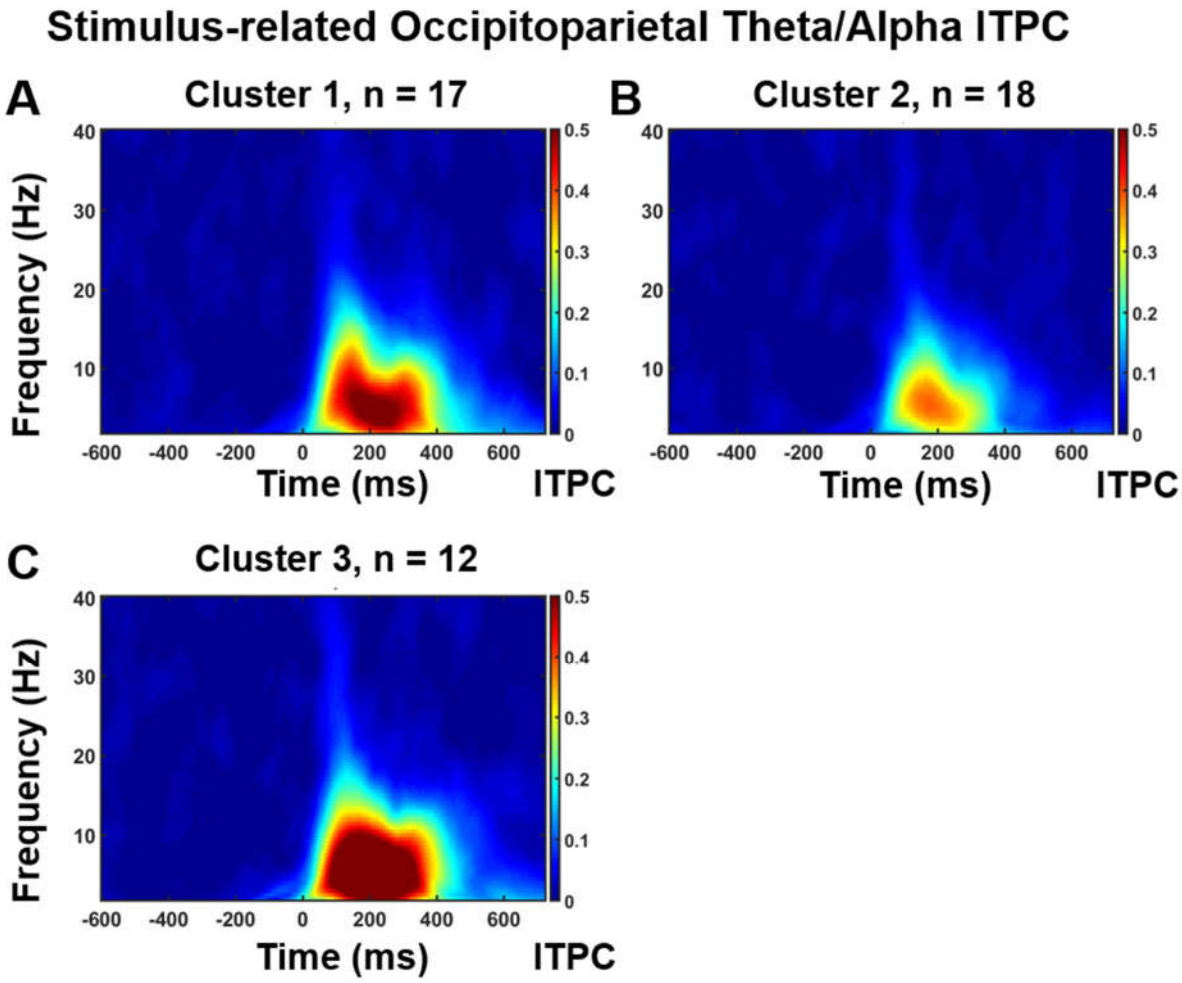

Figure 14. Stimulus-related occipitoparietal theta/alpha ITPC in participants that best fit into A) Cluster 1, B) Cluster 2, C) Cluster 3.

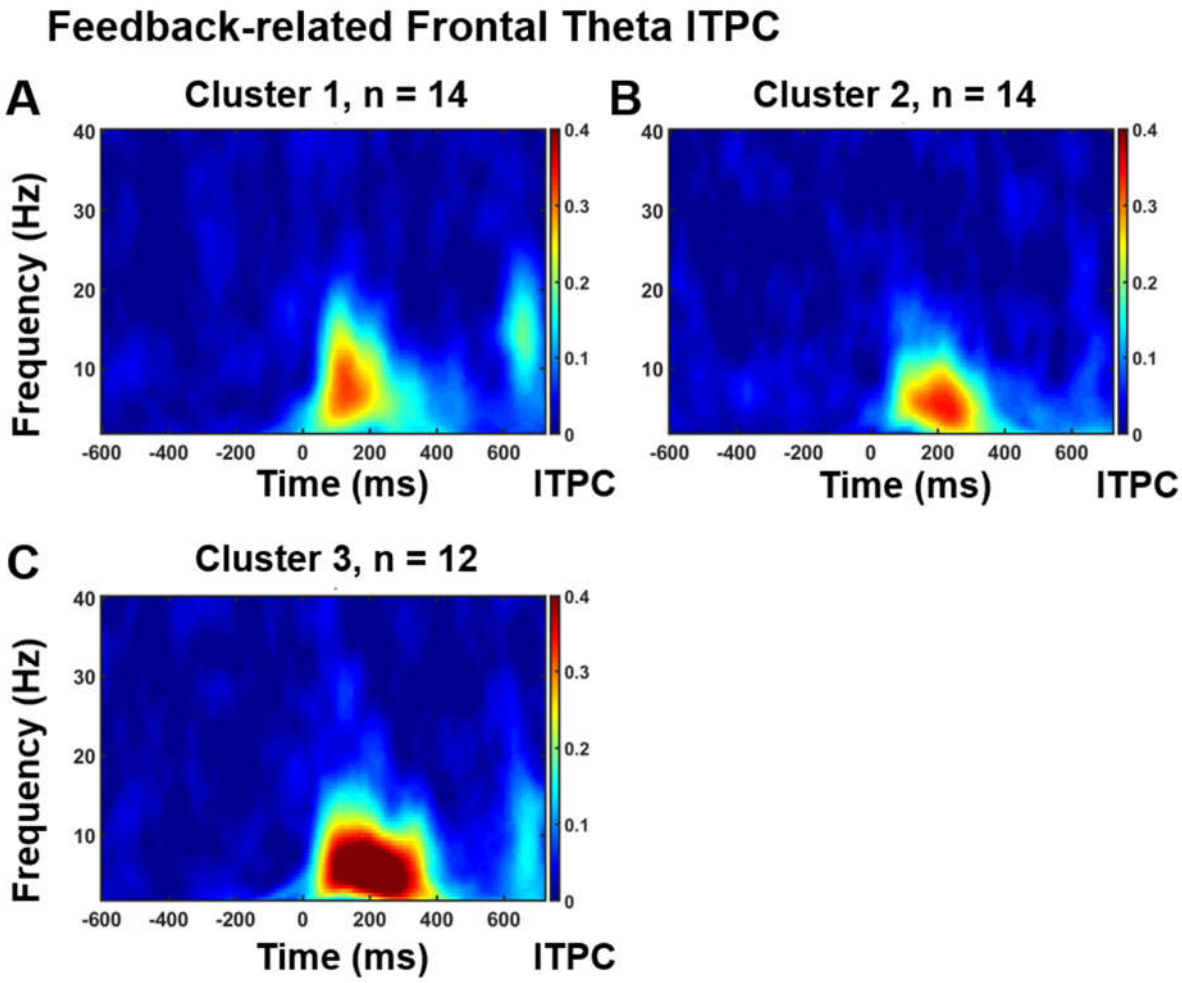

Figure 15. Feedback-related frontal theta/alpha ITPC in participants that best fit into A) Cluster 1, B) Cluster 2, C) Cluster 3.

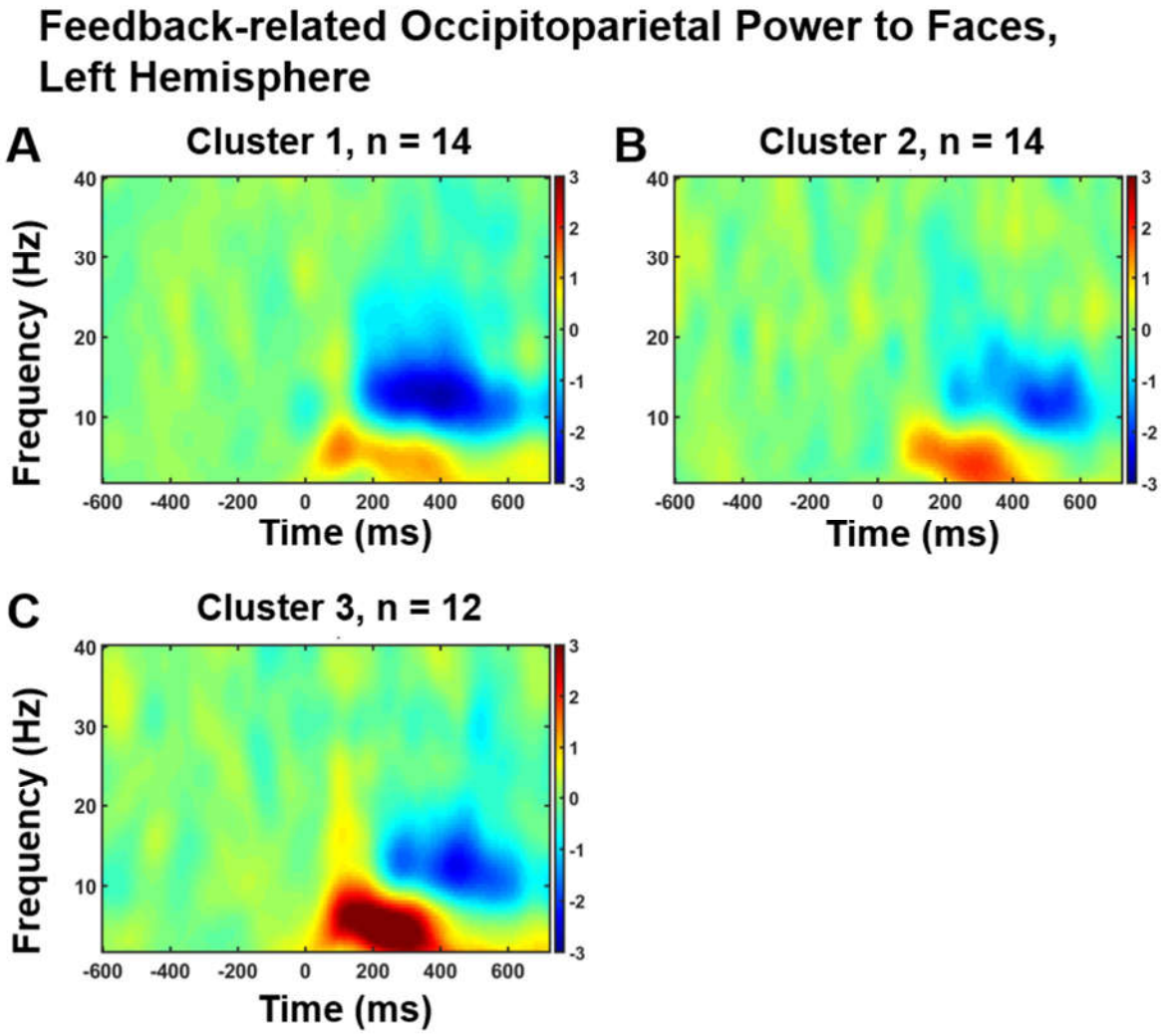

Figure 16. Feedback-related occipitoparietal theta/alpha power in response to faces in the left hemisphere in participants who best fit into A) Cluster 1, B) Cluster 2, and C) Cluster 3.

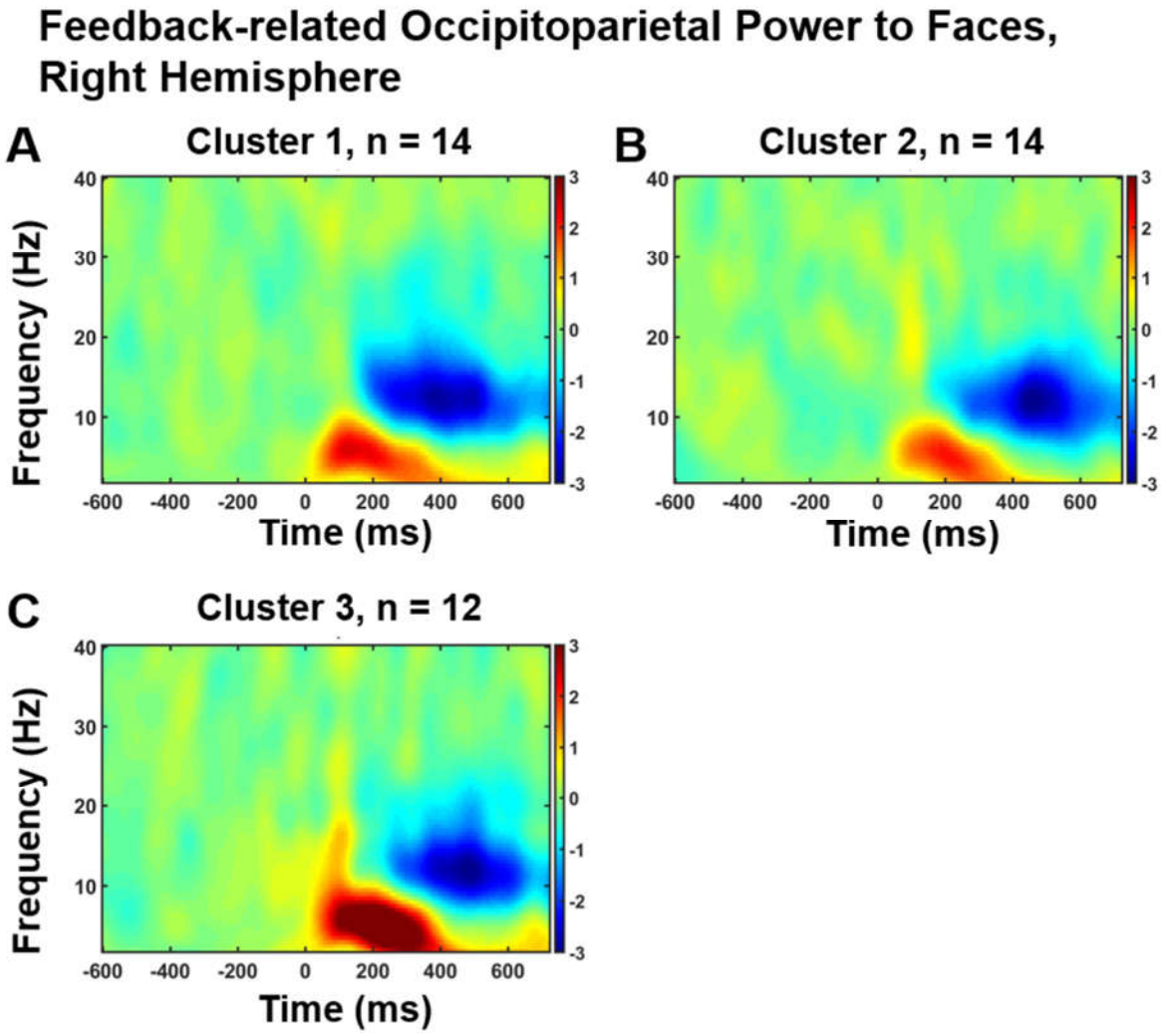

Figure 17. Feedback-related occipitoparietal theta/alpha power in response to faces in the right hemisphere in participants who best fit into A) Cluster 1, B) Cluster 2, and C) Cluster 3.

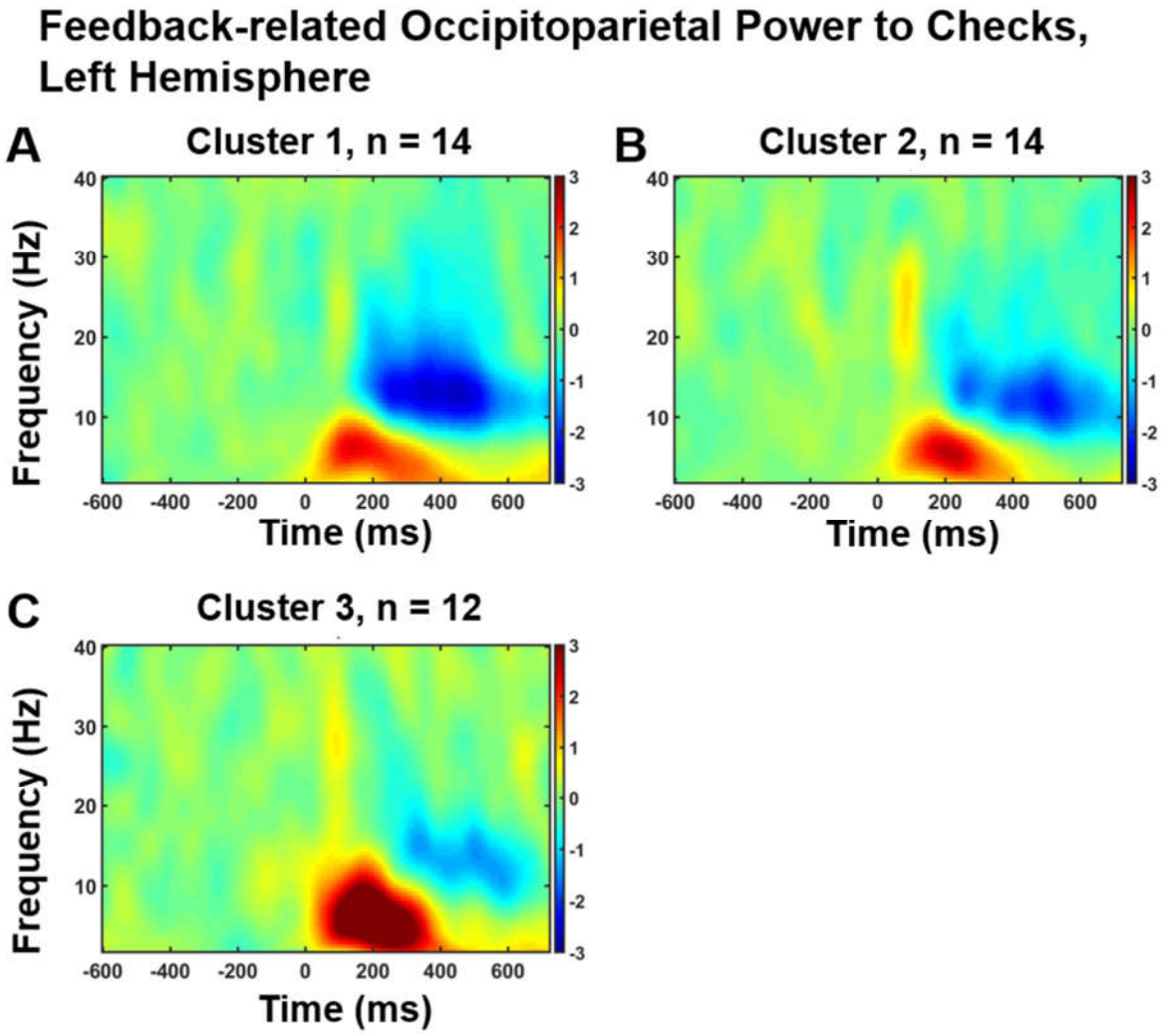

Figure 18. Feedback-related occipitoparietal theta/alpha power in response to checks in the left hemisphere in participants who best fit into A) Cluster 1, B) Cluster 2, and C) Cluster 3.

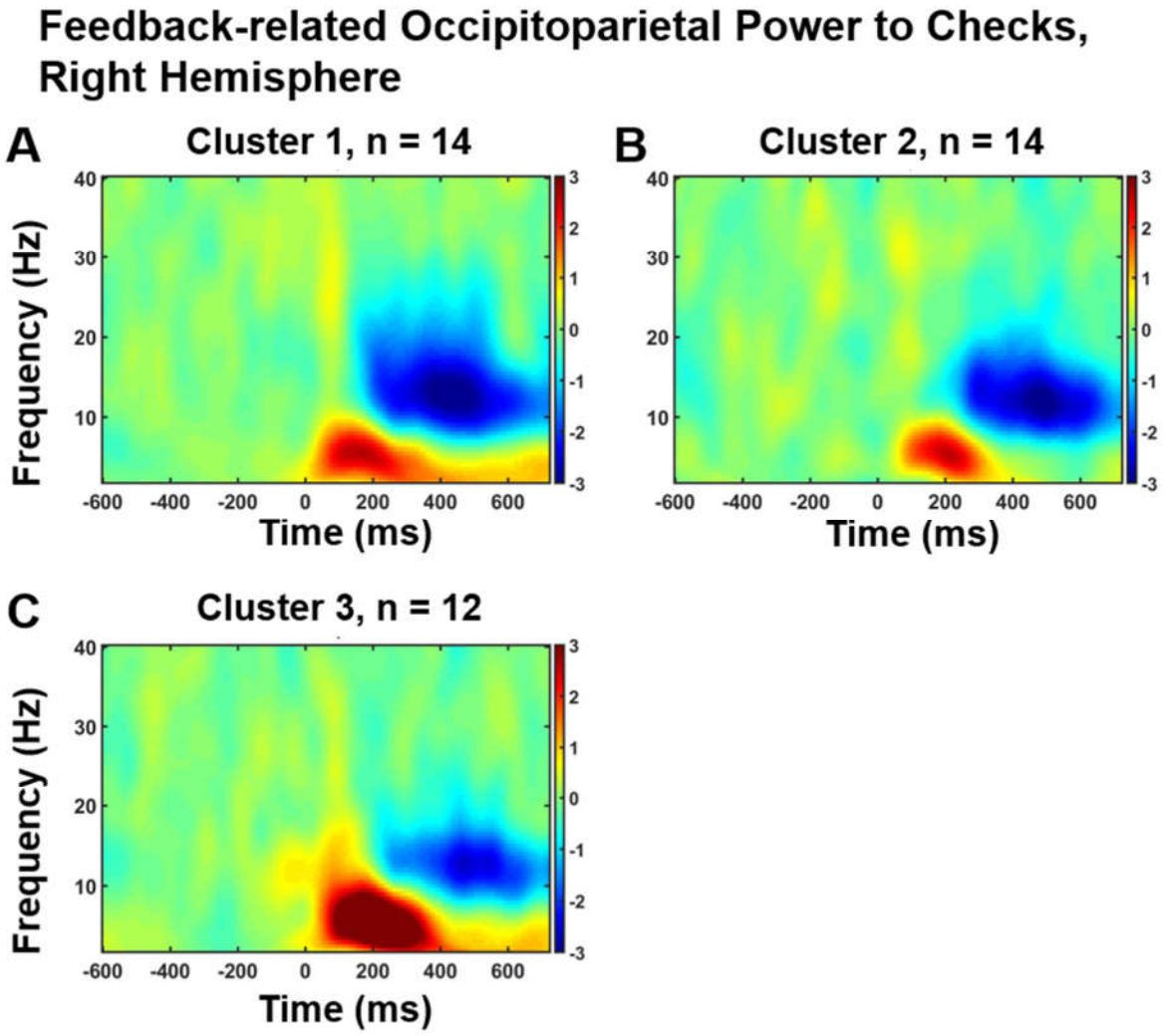

Figure 19. Feedback-related occipitoparietal theta/alpha power in response to checks in the right hemisphere in participants who best fit into A) Cluster 1, B) Cluster 2, and C) Cluster 3.

Tables

Variables of Interest	Disorder	
	ADHD	*ASD*
Resting frontal TBR	Increased	-
*Resting frontal AS**	Increased	-
Resting central high beta/low gamma	-	Increased
RTV	Increased	-
Stimulus-related frontal theta ITPC (200 - 400 ms)	Decreased	-
Stimulus-related occipitoparietal theta/alpha ITPC (0 - 200 ms)	-	Decreased
Pre-feedback frontal AS (-1000 – 0)*	Increased	-
Post-feedback frontal theta ITPC (200 – 400 ms)	Decreased	Decreased
Post-feedback occipitoparietal theta/alpha power difference for faces vs. objects	-	Decreased

Table 1. Variables of interest and hypotheses for each group, relative to TD.

*AS hypotheses suggest increased "rightward" AS, that is, increased alpha power in the right hemisphere.

	Diagnostic Group								
	TDC (n=20)		*ADHD (n=17)*		*ASD (n=5)*		*COM ADHD+ASD (n=8)*		*Analysis*
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age	9.75	2.22	9.12	2.12	8.80	1.92	10.00	1.31	n.s.
K-BIT Nonverbal IQ	106.50	16.94	103.25	17.55	93.80	13.55	97.38	21.70	n.s.
SCQ	2.35	3.31	6.13	4.47	23.60	3.65	18.88	5.69	ASD > ADHD/TDC
PPVT							91.63	9.12	
VABS							75.38	7.23	

Table 2. Demographic information by diagnosis. One participant with ADHD was missing K-BIT Nonverbal IQ and another was missing SCQ score, leaving 16 participants with ADHD for those comparisons. PPVT and VABS were only collected for comorbid participants.

Variable	Cluster 1 *(n = 17)*	Cluster 2 *(n = 20)*	Cluster 3 *(n=13)*
Resting frontal AS	2	2	1
Resting frontal TBR	1	2	1
Resting central gamma	1	2	1
Stimulus-related frontal theta ITPC	0	2	1
Stimulus-related occipitoparietal theta/alpha ITPC, both hemispheres	0	2	1
Pre-feedback AS	1	4	1
Feedback-related frontal theta ITPC	3	6	1
Feedback-related ERS to faces, left hemisphere	3	6	1
Feedback-related ERS to checks, left hemisphere	3	6	1
Feedback-related ERS to faces, right hemisphere	3	6	1
Feedback-related ERS to checks, right hemisphere	3	6	1
Feedback-related ERS ratio of faces/checks, left hemisphere	5	7	1
Feedback-related ERS ratio of faces/checks, right hemisphere	4	7	2
Feedback-related ERD ratio of faces/checks, both hemispheres	3	7	1
Tau for congruent trials	1	2	2
Tau for incongruent trials	1	3	2

Table 3. Number of missing datapoints for each variable, by cluster.

Variable	Demographics		
Effect	**DF**	**F**	**p**
Age			
ADHD	1, 47	.99	.33
ASD	1, 47	.64	.43
K-Bit Nonverbal IQ			
ADHD	1, 46	.09	.77
ASD	1, 46	2.34	.13
SCQ			
ADHD	1, 46	1.46	.23
ASD	1. 46	121.00	**<.0001**

Table 4. ANOVA results for demographic comparisons by diagnosis, with $p \leq .05$ in bold and p $p \leq .10$ in italics.

Variable	Resting		
Effect	DF	F	p
Alpha Asymmetry			
ADHD	1, 42	.51	.48
ASD	1, 42	.46	.50
Theta/Beta Ratio			
ADHD	1, 43	.10	.75
ASD	1, 43	.03	.85
High Beta/Low Gamma Power			
ADHD	1, 43	.04	.85
ASD	1, 43	.01	.90

Table 5. ANOVA results for resting comparisons by diagnosis, with $p \leq .05$ in bold and p $p \leq .10$ in italics.

Variable	Behavior		
Effect	DF	F	p
Accuracy			
ADHD	1,45	2.65	.11
ASD	1, 45	.11	.74
Congruency	1, 45	43.16	**<.0001**
Congruency x ADHD	1, 45	.04	.84
Congruency x ASD	1, 45	.33	.57
Errors of Omission			
ADHD	1, 43	11.10	**.002**
ASD	1, 43	1.24	.27
Congruency	1, 43	2.63	.11
Congruency x ADHD	1, 43	2.52	.12
Congruency x ASD	1, 43	1.02	.32
Mu			
ADHD	1, 38	.04	.84
ASD	1, 38	.16	.69
Congruency	1, 38	20.80	**<.0001**
Congruency x ADHD	1, 38	.18	.68
Congruency x ASD	1, 38	.19	.67
Sigma			
ADHD	1, 38	.07	.79
ASD	1, 38	.52	.48
Congruency	1, 38	7.31	**.01**
Congruency x ADHD	1, 38	.00	.97
Congruency x ASD	1. 38	.36	.55
Tau			
ADHD	1, 38	9.15	**.004**
ASD	1, 38	.23	.64

Congruency	1, 38	10.46	**.003**
Congruency x ADHD	1, 38	.01	.94
Congruency x ASD	1, 38	1.71	.20
EZ-Diffusion Model: *a*			
ADHD	1, 12	.12	.73
ASD	1, 12	.20	.66
Congruency	1, 12	3.70	*.08*
Congruency x ADHD	1, 12	1.30	.28
Congruency x ASD	1, 12	4.02	*.07*
EZ-Diffusion Model: v			
ADHD	1, 12	.72	.41
ASD	1, 12	.33	.58
Congruency	1, 12	13.76	**.003**
Congruency x ADHD	1, 12	.00	.95
Congruency x ASD	1, 12	.13	.72
EZ-Diffusion Model: T_{er}			
ADHD	1, 12	.20	.66
ASD	1, 12	.32	.58
Congruency	1, 12	20.47	**.0007**
Congruency x ADHD	1, 12	.13	.72
Congruency x ASD	1, 12	2.99	.11

Table 6. ANOVA results for behavioral comparisons by diagnosis, with $p \leq .05$ in bold and p $p \leq .10$ in italics.

Variable Effect	Task-Related EEG Variables DF	F	p
Stimulus-Related Frontal Theta ITPC			
ADHD	1, 44	3.11	*.08*
ASD	1, 44	.74	.40
Stimulus-Related Occipitoparietal Theta/Alpha ITPC			
ADHD	1, 44	1.07	.31
ASD	1, 44	.23	.63
Hemisphere	1, 44	.03	.87
Hemisphere x ADHD	1, 44	.86	.36
Hemisphere x ASD	1, 44	.58	.45
Pre-Feedback Frontal Alpha Asymmetry			
ADHD	1, 41	.30	.58
ASD	1, 41	2.12	.15
Feedback-Related Frontal Theta ITPC			
ADHD	1, 37	.03	.87
ASD	1, 37	5.04	**.03**
Sociality	1, 37	1.03	.32
Sociality x ADHD	1, 37	1.15	.29
Sociality x ASD	1, 37	.15	.70
Feedback-Related Occipitoparietal ERS			
ADHD	1, 37	.69	.41
ASD	1, 37	.74	.40
Sociality	1, 37	19.35	**<.0001**
Hemisphere	1, 37	.23	.64
Sociality x ADHD	1, 37	.00	.99
Sociality x ASD	1, 37	.66	.42
Hemisphere x ADHD	1, 37	.98	.33
Hemisphere x ASD	1, 37	4.25	**.046**

Hemisphere x Sociality	1, 37	3.53	*.07*
Hemisphere x Sociality x ADHD	1, 37	2.25	.14
Hemisphere x Sociality x ASD	1, 37	.03	.87
Feedback-Related Occipitoparietal ERS Ratio			
ADHD	1, 31	5.41	**.03**
ASD	1, 31	1.17	.29
Hemisphere	1, 31	.14	.71
Hemisphere x ADHD	1, 31	.26	.62
Hemisphere x ASD	1, 31	.44	.51
Feedback-Related Occipitoparietal ERD			
ADHD	1, 37	1.11	.30
ASD	1, 37	.82	.37
Sociality	1, 37	.57	.46
Hemisphere	1, 37	8.08	**.007**
Sociality x ADHD	1, 37	.09	.76
Sociality x ASD	1, 37	1.05	.31
Hemisphere x ADHD	1, 37	.37	.55
Hemisphere x ASD	1, 37	.48	.49
Hemisphere x Sociality	1, 37	1.84	.18
Hemisphere x Sociality x ADHD	1, 37	.09	.76
Hemisphere x Sociality x ASD	1, 37	.41	.53
Feedback-Related Occipitoparietal ERD Ratio			
ADHD	1, 33	3.61	*.07*
ASD	1, 33	.14	.71
Hemisphere	1, 33	1.20	.28
Hemisphere x ADHD	1, 33	1.71	.20
Hemisphere x ASD	1, 33	.74	.40

Table 7. ANOVA results for task-related EEG comparisons by diagnosis, with $p \leq .05$ in bold and $p \leq .10$ in italics.

Variable	Cluster 1	Cluster 2	Cluster 3
Resting frontal AS	-.43	.87	.63
Resting frontal TBR	-.02	-.35	.69
Resting central gamma	.12	.29	-.73
Stimulus-related frontal theta ITPC	-.08	-1.03	.84
Stimulus-related occipitoparietal theta/alpha ITPC, both hemispheres	.10	-.74	1.02
Pre-feedback AS	-.21	.40	.19
Feedback-related frontal theta ITPC	-.67	-.08	.93
Feedback-related ERS to faces, left hemisphere	-.34	.16	1.09
Feedback-related ERS to checks, left hemisphere	-.38	-.11	1.05
Feedback-related ERS to faces, right hemisphere	-.34	-.29	.74
Feedback-related ERS to checks, right hemisphere	-.30	-.07	.97
Feedback-related ERS ratio of faces/checks, left hemisphere	-.15	-.05	-.24
Feedback-related ERS ratio of faces/checks, right hemisphere	.05	-.20	-.09
Feedback-related ERD ratio of faces/checks, both hemispheres	-.16	-.72	.65
Tau for congruent trials	-.53	1.49	0.16
Tau for incongruent trials	-.25	1.80	-.29

Table 8. Cluster means for each variable submitted to cluster analysis.

Diagnosis	Cluster 1	Cluster 2	Cluster 3	Total
TDC	11	4	5	20
ADHD	4	10	3	17
ASD	0	2	3	5
COM	2	4	2	8
Total	17	20	13	50

Table 9. Cluster membership by diagnosis.

	Cluster						
	Cluster 1 (n=17)		*Cluster 2 (n=20)*		*Cluster 3 (n=13)*		*Analysis*
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age	9.94	1.92	8.60	2.09	8.69	1.84	n.s.
K-BIT Nonverbal IQ	110.94	14.36	96.58	17.05	100.69	19.52	Cluster 1 > Cluster 2
SCQ	6.12	6.98	9.21	8.62	10.38	10.67	n.s.
PPVT	92.50	4.95	85.25	2.99	103.50	9.19	
VABS	72.00	12.73	75.25	4.35	79.00	9.90	

Table 10. Demographic information by cluster. One participant in Cluster 2 is missing K-BIT Nonverbal IQ and another is missing SCQ score, leaving 19 participants for those comparisons. PPVT and VABS were only collected for comorbid participants (n=8) so no statistical comparisons were performed.

Variable	Before Addition of COM (n = 42)			After Addition of COM (n = 50)		
Effect	**DF**	**F**	**p**	**DF**	**F**	**p**
Age						
Cluster	2, 39	1.97	.15	2, 47	2.47	*.10*
K-Bit Nonverbal IQ						
Cluster	2, 38	1.42	.25	2, 46	3.37	**.04**
SCQ						
Cluster	2, 38	1.02	.37	2, 46	1.00	.37
Accuracy						
Cluster	2, 37	5.95	**.006**	2, 45	10.99	**.0001**
Congruency	1, 37	47.75	**<.0001**	1, 45	61.69	**<.0001**
Cluster x Congruency	2, 37	1.16	.33	2, 45	1.32	.28
Errors of Omission						
Cluster	2, 36	5.27	**.01**	2, 43	10.14	**.0002**
Congruency	1, 36	1.47	.23	1, 43	2.14	.15
Cluster x Congruency	2, 36	1.35	.27	2, 43	.79	.46

Table 11. ANOVA results for demographic, clinical, and behavioral comparisons across clusters, before (left) and after (right) COM participants were added to the cluster, with $p \leq .05$ in bold and $p \leq .10$ in italics.

Variable	Function 1 Stimulus Engagement	Function 2 Feedback Responsivity
Stimulus-related frontal theta ITPC	**.32**	.16
Stimulus-related occipitoparietal theta/alpha ITPC, both hemispheres	**.31**	.15
Feedback-related ERD ratio of faces/checks, both hemispheres	**.22**	.12
Feedback-related ERS to checks, right hemisphere	.18	**.34**
Feedback-related ERS to faces, right hemisphere	.16	**.24**
Resting frontal TBR	**.15**	.12
Feedback-related ERS to checks, left hemisphere	.15	**.33**
Feedback-related frontal theta ITPC	.11	**.53**
Feedback-related ERS to faces, left hemisphere	.11	**.36**
Pre-feedback AS	.05	**.06**
Feedback-related ERS ratio of faces/checks, right hemisphere	.02	**-.04**
Resting frontal AS	-.01	**.15**
Feedback-related ERS ratio of faces/checks, left hemisphere	**-.02**	.00
Resting central gamma	-.13	**-.17**
Tau for incongruent trials	**-.41**	.18
Tau for congruent trials	**-.43**	.41

Table 12. Canonical correlations of each variable with each function, ordered by most positive relationship with function 1 to least. The largest correlation is listed in bold.

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