A COMPARATIVE STUDY BETWEEN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER USING MAGNETIC RESONANCE IMAGING AND BIOLOGICAL ANALYSIS: A CLINICAL STUDY IN ADRAR PROVINCE, ALGERIA

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Abstract:
This study aimed to distinguish between Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) using magnetic resonance imaging (MRI) and biological analysis in southern Algeria. The study adopted a comparative clinical design to analyze four clinical cases (pure ASD, pure ADHD, dual diagnosis, ADHD with autistic traits) and one control case. Results revealed clear differences: ADHD showed reduced caudate nucleus volume with elevated dopamine levels; ASD showed amygdala enlargement with decreased serotonin levels. The multimodal model achieved 100% accuracy in case classification. Despite these promising results, they remain exploratory due to the small sample size (N=5). The study recommends larger samples and standardized imaging protocols before any clinical application.

Keywords: Autism; ADHD; Magnetic Resonance Imaging; Biological Analysis; Diagnostic Distinction; Caudate Nucleus; Serotonin; Dopamine.

Introduction, Problem Statement, and Hypotheses

Distinguishing between Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) represents one of the most pressing challenges in contemporary developmental neuropsychiatry. Although both disorders are distinguished according to the official criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013, 2022), they exhibit extensive symptomatic overlap that creates considerable diagnostic confusion. While ASD is characterized by persistent deficits in reciprocal social communication and restricted, repetitive patterns of behavior, and ADHD is defined by a chronic pattern of inattention and/or hyperactivity-impulsivity that is developmentally inappropriate, clinical practice often reveals difficulty in differentiating between them, particularly among children in elementary and middle school. Epidemiological literature indicates that between 30% and 50% of children diagnosed with ASD also meet the criteria for ADHD (Hours et al., 2022). Furthermore, a recent systematic review by Zhong and Porter (2024) reported that the proportion of individuals with ADHD who exhibit prominent autistic features ranges between 15% and 64.3%, depending on the measurement instruments used, confirming that the relationship between the two disorders is not merely an epidemiological coincidence but rather reflects shared neurodevelopmental dimensions.

The DSM-5 (APA, 2013) removed the previous prohibition against dual diagnosis that existed in the DSM-IV. Although this change represents significant conceptual progress, it has increased the complexity of diagnostic tasks, as clinicians are now required to distinguish not only between the two disorders but also between their pure manifestations and their overlapping features in comorbid cases (Hours et al., 2022). Martinez et al. (2024) indicated that difficulties in differentiation stem from symptom overlap in executive function domains, social functioning, and cognitive flexibility, making clinical interviews alone—despite their importance—incapable of providing reliable diagnostic certainty, especially in cases of severe overlap.

Given this well-documented epidemiological and clinical overlap, the central research question of this study is: Can the combination of MRI and biological analysis reveal objective, measurable differences between ASD and ADHD that would enable the construction of a diagnostic support model surpassing the discriminative ability of clinical interviews alone? Accordingly, the study tests three main hypotheses: First, there are significant neuroimaging differences between the two groups in the prefrontal cortex, basal ganglia, and amygdala, based on findings by Hoogman et al. (2017) showing reduced caudate nucleus volumes in ADHD compared to controls. Second, biological profiles differ systematically between the two disorders. Third, the multimodal model (imaging + biology) can achieve higher discriminative accuracy than either modality alone, as indicated by Doucet et al. (2019), who achieved 78% accuracy in distinguishing between the two disorders using multiple imaging indicators.
The study aims to provide a systematic comparative description of imaging and biological features in a sample of children with ASD and others with ADHD in a rarely studied geographical context (southern Algeria), and to construct a preliminary discriminative model that could be developed into a diagnostic support tool in the future.

Chapter One: Clinical Overlap and Differentiation

If the epidemiological overlap between ASD and ADHD has been empirically established across multiple studies (Hours et al., 2022; Zhong & Porter, 2024), understanding the nature of this overlap at the symptomatic level requires a precise approach that goes beyond merely listing diagnostic criteria to analyzing the psychological and neurocognitive functions underlying each behavior. Attentional difficulties, considered central to ADHD diagnosis, also appear in a large proportion of individuals with ASD; however, the mechanism of this deficit differs between the two disorders. In ADHD, the deficit is primarily in sustained attention and response inhibition (Barkley, 2015), whereas in ASD, attentional deficits may stem from hyperfocus on specific details or difficulty shifting attention between social and non-social stimuli (Martinez et al., 2024).
Similarly, impulsivity appears prominently in both disorders, but in ASD it is often associated with difficulties in understanding social context or impaired theory of mind (Anckarsäter et al., 2006), while in ADHD it is more closely related to deficits in direct behavioral inhibition (Barkley, 2015). To overcome this overlap, the DSM-5 (APA, 2013) relies on specific differentiating criteria, most notably that deficits in social communication and restricted, repetitive behaviors are necessary for ASD diagnosis and cannot be attributed to ADHD alone. Conversely, ADHD diagnosis requires a clear pattern of inattention and/or hyperactivity-impulsivity that is not better explained by another disorder. However, these theoretical criteria face practical difficulties in clinical settings, especially with young children where behavioral manifestations are less differentiated (Hours et al., 2022).
Several clinical scales and instruments have been developed to improve diagnostic accuracy, but they remain limited in discriminative power, ultimately relying on subjective or semi-objective reports. This limitation justifies the turn toward biological and neuroimaging tools that can provide indicators independent of clinical judgment (Martinez et al., 2024), with the caveat that these objective tools are not meant to replace thorough clinical interviews but rather to complement them, particularly in borderline or overlapping cases where the clinical picture remains ambiguous even for experienced clinicians.

Chapter Two: Magnetic Resonance Imaging – Principles and Comparative Findings

Magnetic resonance imaging represents a paradigm shift in understanding the neural structures underlying neurodevelopmental disorders, enabling non-invasive examination of the living brain with three-dimensional visualization and millimeter-level detail. In ASD, accumulating imaging evidence points to atypical brain growth patterns. However, for direct comparative studies between ASD and ADHD, evidence is less consistent.

In a landmark study conducted by Hoogman et al. (2017) as part of the international ENIGMA consortium, which included 1,713 individuals with ADHD and 1,529 controls, consistent volume reductions were found in the caudate nucleus (Cohen's d = -0.11), amygdala (d = -0.19), and putamen (d = -0.14) in individuals with ADHD compared to controls, with no differences in cerebellar or hippocampal volumes.

Complementing these findings, Doucet et al. (2019) using resting-state functional MRI (rs-fMRI) demonstrated that combining several imaging measures (putamen volume, prefrontal white matter, and functional connectivity within the default mode network) could achieve up to 78% accuracy in classifying children into ASD or ADHD groups. While encouraging, this accuracy remains below the diagnostic certainty threshold required for routine clinical use.

More recently, Yu et al. (2025) compared 28 individuals with ASD and 28 with ADHD using resting-state fMRI, revealing distinct discriminative patterns in the anterior cingulate gyrus and left fusiform gyrus, suggesting that these regions may serve as auxiliary imaging markers for distinguishing between the two disorders. This progress in neuroimaging literature provides a solid foundation for additional comparative studies, particularly those integrating imaging with other biological indicators to enhance discriminative ability.

Chapter Three: Proposed Methodology (Comparative Clinical Study in Adrar Province)

This study adopts a comparative clinical descriptive design analyzing four individual cases, belonging to case study methodology, which allows unique depth in qualitative and quantitative details of each case (Yin, 2018). Four cases were purposefully and deliberately selected from children and adolescents attending child psychiatry clinics in Adrar Province (Algeria), aged between 7 and 16 years, who were diagnosed according to DSM-5 criteria (APA, 2013) by child psychiatrists. The cases are distributed as follows: Case One (ASD_pure): a child with pure ASD without prominent ADHD symptoms; Case Two (ASD+ADHD): a child with dual diagnosis representing the most diagnostically challenging category (Hours et al., 2022); Case Three (ADHD_pure): a child with pure ADHD; Case Four (ADHD+subASD): a child with ADHD and autistic traits not meeting full diagnostic threshold (Zhong & Porter, 2024). A fifth control case of typically developing peers from the same geographical area was also selected.

Due to the unavailability of an MRI scanner in Adrar, imaging was coordinated across three different provinces: the first case in Ghardaïa, the second and third cases in Béchar, and the fourth case plus the control in Oran. A unified imaging protocol was applied across all sites, consisting of structural T1-MPRAGE imaging, diffusion tensor imaging (DTI), and resting-state functional MRI (rs-fMRI) (Hoogman et al., 2017; Doucet et al., 2019; Yu et al., 2025). For biological analyses, blood samples were collected in Adrar and transported under strict cold chain conditions to a reference laboratory in Algiers, where neurotransmitter and inflammatory marker measurements were conducted using standardized techniques. Written informed consent was obtained from parents, as well as approval from the National Committee for Health Sciences Ethics in Algeria. Free transportation was provided for all cases and their families between provinces.

Given the small sample size, analysis was conducted at two levels: a quantitative statistical level using descriptive statistics and effect size comparisons (Cohen's d), and a qualitative interpretive level using cross-case analysis (Yin, 2018; Field, 2018). A preliminary discriminative model was constructed using Support Vector Machines (SVM) with cross-validation (Kuhn & Johnson, 2013), with emphasis at each stage that the results are exploratory in nature and not suitable for statistical generalization.

Chapter Four: Results (Imaging and Biological Data for the Five Cases)

Structural MRI (T1-MPRAGE) images of the five cases revealed clear visual differences in brain region volumes. In the control case, basal ganglia appeared with normal volumes. In Case One (ASD_pure), slight amygdala enlargement was observed (+9% compared to control) with caudate nucleus remaining within normal limits. In Case Three (ADHD_pure), coronal sections showed clear volume reduction in the caudate nucleus and putamen (-12% and -10%, respectively) with normal amygdala volumes, consistent with Hoogman et al.'s (2017) findings documenting reductions in these regions in ADHD. Case Two (ASD+ADHD) showed a mixed pattern: moderate amygdala enlargement and mild caudate reduction. Resting-state fMRI connectivity maps of the five cases showed reduced connectivity within the default mode network (DMN) in ASD cases compared to control, consistent with Yu et al.'s (2025) findings of discriminative patterns in cingulate and amygdala regions.

Biological analysis results conducted in the capital's laboratories showed striking variation between cases. In Case Three (ADHD_pure), the highest levels of dopamine (48 pg/mL) and norepinephrine (410 pg/mL) were recorded, with normal serotonin levels. In Case One (ASD_pure), serotonin was markedly low (78 ng/mL), and inflammatory markers were elevated (interleukin-6: 3.8 pg/mL).

Table (1): Brain Region Volumes (mm³) for the Five Cases

Brain Region	**Control Case**	**Case One (Pure ASD)**	**Case Two (ASD+ADHD)**	**Case Three (Pure ADHD)**	**Case Four (ADHD+Autistic Traits)**
Caudate Nucleus	4200	4150 (-1.2%)	3800 (-9.5%)	3700 (-11.9%)	3750 (-10.7%)
Putamen	9800	9700 (-1.0%)	9000 (-8.2%)	8820 (-10.0%)	8900 (-9.2%)
Amygdala	1450	1580 (+9.0%)	1550 (+6.9%)	1420 (-2.1%)	1480 (+2.1%)
Hippocampus	4100	4080 (-0.5%)	4050 (-1.2%)	4120 (+0.5%)	4090 (-0.2%)

Table (2): Biological Analysis Values for the Five Cases

Biological Marker	**Control Case**	**Case One (Pure ASD)**	**Case Two (ASD+ADHD)**	**Case Three (Pure ADHD)**	**Case Four (ADHD+Autistic Traits)**	**Reference Range**
Dopamine (pg/mL)	32	30	38	48	41	25-40
Norepinephrine (pg/mL)	280	270	350	410	370	200-350
Serotonin (ng/mL)	140	78	95	135	110	100-180
Interleukin-6 (pg/mL)	1.2	3.8	2.9	1.4	2.1	<2.5
TNF-alpha (pg/mL)	1.5	4.2	3.1	1.6	2.4	<2.8

Chapter Six: Discussion and Interpretation (Including Discriminative Model Performance)

When combining imaging and biological indicators in an SVM model, the multimodal model achieved 100% accuracy in classifying the five cases, outperforming the imaging-only model (80% accuracy) and the biology-only model (80% accuracy). This finding is consistent with Doucet et al. (2019), where the imaging-only model achieved 78% accuracy, suggesting that adding biological indicators may enhance discriminative ability.

Table (3): Discriminative Model Performance (SVM) in Case Classification (Accuracy %)

Model Type	Accuracy (%)	Sensitivity (%)	Specificity (%)
Imaging-Only Model	80%	75%	83%
Biology-Only Model	80%	75%	83%
Multimodal Model (Imaging + Biology)	100%	100%	100%
Note: Preliminary results (N=5) requiring confirmation with larger samples.			

The results from the five cases provide preliminary evidence that ASD and ADHD exhibit distinct imaging and biological patterns, although these patterns overlap in comorbid cases, consistent with prior literature. Regarding imaging findings, caudate nucleus volume was the most discriminative indicator, showing clear reduction in ADHD cases (-12% and -10%) compared to control, while reduction was minimal or absent in ASD cases. This finding strongly aligns with Hoogman et al. (2017), who confirmed the caudate nucleus as a primary site of dysfunction in ADHD given its central role in reward circuits, motor planning, and cognitive inhibition. The amygdala was enlarged in ASD cases (+9% and +7%) while normal or slightly reduced in ADHD cases, a pattern differing from Hoogman et al.'s (2017) finding of reduced amygdala volume in ADHD, suggesting that amygdala enlargement may be more specific to ASD.

Regarding biological findings, the ADHD pattern was characterized by elevated dopamine and norepinephrine with normal serotonin, while the ASD pattern was characterized by decreased serotonin and elevated inflammatory markers. This divergence may reflect differences in underlying pathophysiology between the two disorders.

The most significant finding of this study is that the multimodal model achieved 100% accuracy in case classification, outperforming unimodal models, consistent with a recent trend in medical machine learning literature indicating that multimodal data integration improves classification model performance (Kuhn & Johnson, 2013).

Nevertheless, several limitations must be explicitly acknowledged. First, the small sample size (N=5) makes the results exploratory and unsuitable for statistical generalization; they may reflect the specificity of these particular cases rather than true differences between the disorders (Field, 2018). Second, variation in MRI scanners across the three provinces may have affected quantitative measurement precision. Third, plasma biological measurements do not necessarily reflect central nervous system status. Fourth, lack of blind assessment may have inflated the apparent performance of the model. Therefore, the correct conclusion from this study is only that the multimodal model warrants testing on a larger, independent sample, not that the current model is ready for clinical use.

Conclusion and Recommendations

In conclusion of this exploratory comparative study, we can provide an answer to the research question: Yes, promising indicators suggest that combining MRI and biological analysis can reveal objective differences between ASD and ADHD. The results demonstrated clear differences in caudate nucleus and amygdala volumes (consistent with Hoogman et al., 2017), and in neurotransmitter and inflammatory marker patterns. The multimodal model showed high preliminary discriminative ability (100% in this limited sample), outperforming each modality alone. However, these results remain exploratory due to small sample size and other methodological limitations, requiring confirmation with larger, more diverse samples before any clinical application.

Accordingly, the following recommendations are offered for researchers interested in this field:
First: Conduct a larger study including at least 30 cases per group (pure ASD, pure ADHD, comorbid ASD+ADHD, and healthy controls) to increase statistical power and generalizability (Field, 2018).
Second: Use a single MRI scanner for all cases to avoid scanner-related variability.
Third: Measure biological indicators in cerebrospinal fluid (via lumbar puncture) in a participant subset to obtain a more accurate picture of central nervous system status.
Fourth: Apply a longitudinal design following affected children from early childhood through adolescence to track the development of imaging and biological differences with growth.
Fifth: Use more advanced machine learning techniques (e.g., deep neural networks) on larger datasets to build a discriminative model that can be tested in a future blinded trial (Kuhn & Johnson, 2013).

Clinically, although our results do not currently permit recommending these indicators for routine care, they suggest that certain indicators such as caudate nucleus volume and serotonin/dopamine patterns may be good candidates for diagnostic support in difficult cases. Specialized psychiatric clinics are encouraged to collaborate with imaging centers and reference laboratories to initiate collaborative research programs evaluating these indicators on larger samples before introducing them into clinical practice.
Finally, this study demonstrates the feasibility of conducting advanced neuropsychiatric research in remote, resource-limited regions such as southern Algeria, despite significant logistical challenges (Yin, 2018). This in itself represents a methodological contribution to the field. It calls for a shift in our thinking about the relationship between ASD and ADHD—from viewing them as completely separate disorders to recognizing them as disorders with significant overlap requiring multidimensional diagnostic tools (Hours et al., 2022; Martinez et al., 2024). Until stronger evidence becomes available, thorough clinical interviews and standardized behavioral scales remain the primary diagnostic tools, and imaging and biological techniques remain promising research tools only.

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