Effect of co-occurring conditions on the pediatric manifestations of catatonia: systematic analysis of individual patient data

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Abstract

Importance:

Catatonia is a rare psychomotor syndrome, of which three main subtypes are described, "excited", "retarded" and "malignant". Its diagnosis is challenging in pediatric patients, due to its multitude of presentations, and the overlap of its symptoms with those of the co-occurring conditions. Improved knowledge of the impact of co-occurring conditions on the symptoms of catatonia would allow a more precise diagnosis.

Objective

To investigate the impact of developmental and psychiatric co-occurring conditions, or of their absence (unspecified catatonia) on the symptoms of catatonia, age of occurrence and sex-ratio in pediatric patients. For comparison purposes, patients with catatonia following NMDAR-antibody encephalitis (NMDARE), were included in the analyses, as a model of a medical condition with a known neurotransmitter-related mechanism.

Data Sources:

We searched PubMed, EMBASE and PsychINFO for studies published between January 1, 1995, and September 10, 2021.

Study Selection:

case-reports of patients under 18 years old with catatonia and the selected co-occurring conditions.

Data Extraction and Synthesis:

Co-occurring conditions, catatonia DSM-5 diagnostic criteria and “malignant” symptoms, age at first catatonic signs and sex were individually extracted. From these symptoms, we inferred the "excited", "retarded" and "malignant" catatonia subtypes.

Main Outcome and Measure:

We estimated the effect of co-occurring conditions on the catatonia symptoms and subtypes.

Results

On 1,425 study records,184 (237 patients) were eligible for analysis. The median age was 15 years old. There was a higher ratio of males to females in all conditions except for NMDARE. The "excited" form was more common in neurodevelopmental conditions (beta = 0.608, 95%CI: 0.416, 0.799), psychiatric conditions (beta = 0.261, 95%CI: 0.093, 0.429), and NMDARE (beta = 0.266, 95%CI: 0.047, 0.485), than in “unspecified catatonia” (beta=-0,062, 95%CI: -0.236, -0.112); the "retarded" form was more prevalent in psychiatric disease (beta = 0.291, 95%CI: 0.099, 0.483) and less in the medical condition (beta=-0.592, 95%CI: -0.846, -0.339). The "malignant" form was found more in psychiatric (beta = 0.367, 95%CI: 0.230, 0.505) and medical conditions (beta = 0.861, 95%CI: 0.632, 1.090), and less in unspecified condition (beta=-0.551, 95%CI: -0.687, -0.415). Within the different types of catatonia, some symptoms were more specific to one condition. Overall, stupor, mutism and negativism were the symptoms most independent of co-occurring conditions.

Conclusions and Relevance:

Searching for catatonic symptoms most frequently associated with a specific condition may unravel a catatonia otherwise unnoticed. Conversely, analyzing catatonic symptoms may help the clinician in the search for co-occurring conditions.

Key Points

Question: How do co-occurring neurodevelopmental, psychiatric, and medical conditions determine the pediatric manifestations of catatonia?

Findings: The "retarded", "excited" and "malignant" subtypes as well as the DSM-5 symptoms of catatonia are distinctively associated with neurodevelopmental, psychiatric, and medical conditions.

Meaning: Analysis of the symptoms of catatonia guides the diagnosis of co-occurring diseases and comorbidities.

INTRODUCTION

Catatonia is a neuropsychiatric syndrome defined by motor (decreased, increased, or abnormal psychomotor activity), speech and behavioral symptoms[1]. While Emil Kraepelin and Eugen Bleuler’s early observations associated catatonia with psychiatric disorders, particularly schizophrenia[2,3], it is now recognized that catatonia occurs in different conditions: bipolar disorder (BD), neurodevelopmental disorders (ND) (mostly autism spectrum disorder (ASD) and intellectual disability) and general medical conditions[4]. Among those, the NMDA receptor antibody encephalitis (NMDARE)[5] represents a potential neurobiological model of catatonia, as its neuroreceptor-related mechanism is identified[6,7]. ICD-11 now presents catatonia as an independent diagnostic entity, irrespective of its co-occurring conditions[8].

The variability of the catatonia presentations is explained by the use of polythetic criteria: a DSM-5 diagnosis of catatonia requires 3 out of 12 signs with equivalent weight, resulting in 4,017 different combinations consistent with its diagnosis[9]. Although there is no consensus on the nosology of catatonia[4,5,10–12] "retarded" and "excited" subtypes are commonly described[11,13,14]. A "malignant" subtype of catatonia has also been described[13], possibly associated with the "excited" subtype[14] a poorer prognosis and frequent medical complications[15].

An intrinsic difficulty in detecting the signs whose grouping allows a diagnosis of catatonia is to distinguish them from those of the pre-existing conditions. This is especially challenging for differentiating stereotypies linked to autism or catatonia, or agitation related to BD, physical discomfort or catatonia. Clinicians are expected to detect symptoms pertaining to catatonia by comparing them to the baseline symptoms, and by their temporal coincidence with other, non-overlapping symptoms[16]. This is however of no help when the associated condition presents with high level of poorly distinct motor symptoms, or when the onset of catatonic symptoms is insidious and quasi-chronic[17], at odds with the acute course previously described when catatonia occurs during the course of psychiatric disorders[2]. The influence of premorbid conditions on catatonic presentations is yet an uncharted territory. Few studies had sufficient sample-size to conduct statistical comparisons between associated conditions, and those studies with the larger sample-sizes focused on one condition only, for example ASD, n = 22[18] or NMDARE, n = 57[5], and did not include patients with other conditions to compare their symptoms.

In this systematic review, we examine how co-occurring conditions influence the manifestation of subtypes and DSM-5 symptoms of catatonia occurring during the course of neurodevelopmental and psychiatric conditions, unspecified (without known conditions), and in patients with NMDARE. As secondary outcomes, we examined the influence on other co-occurring symptoms or characteristics: sleep disorder, hypophagia, self-harm behaviour, and age of occurrence, as neurodevelopmental and medical co-occurring disorders have been reported more frequently in children and adolescents with catatonia[4,19].

METHODS

Search strategy and selection criteria

We searched PubMed, EMBASE and PsychINFO on September 10, 2021, for studies published since January 1, 1995 (following the DSM-IV publication), using keywords and index terms, in the overall form: (catatonia AND (child OR adolescent) AND (case report))(full search strategy in Supplement 1). Two reviewers independently screened titles and abstracts (VRB and EFBX). Full texts from selected abstracts were then inspected for inclusion by one reviewer (IB). All final decisions were confirmed by a second reviewer (VRB). Inclusion criteria were: studies published in English or French, featuring cases aged < 18 years old at reported diagnosis of catatonia, and presenting at least 1 of the 12 DSM-5 criteria. We further extracted the DSM-5 diagnostic signs reported for each patient. Individuals with 1 or 2 catatonic criteria

(hereby, "subthreshold" catatonia) were separately processed from those with 3 or more criteria warranting a full DSM-5 diagnosis. Among medical causes of catatonia, we included NMDARE[5], confirmed by the detection of auto-antibodies in the cerebrospinal fluid, whose relative frequency allows statistical comparison[20,21]. Catatonia due to another medical condition to which the symptoms could plausibly be assigned[22], such as encephalopathy, encephalitis, traumatic injury, vascular, neoplastic, toxic, metabolic, auto-inflammatory, or infectious conditions were excluded as they were too heterogeneous to be meaningfully grouped, or too rare to allow statistical comparison. This systematic review protocol was prospectively registered on PROSPERO international registry (CRD42020187529) and adhered to the PRISMA guidelines.

Data extraction

One reviewer (IB) extracted age at the first consultation for catatonia, age, sex, symptoms of catatonia according to DSM-5 and co-occurring conditions known to be associated with catatonia[10,19,23,24]: (1) neurodevelopmental disorders, including ASD (and age at diagnosis), intellectual disability (IQ < 70), and genetic diagnoses; (2) psychiatric disorders, including psychotic disorder (prior or current), bipolar disorder, depressive disorder (prior or current depressive episode but no manic episode), and medical conditions, here restricted to NMDAR-antibody encephalitis. "Catatonia unspecified" was defined as the absence of all the above. A second reviewer (VRB) independently extracted a random sample of 10% of all cases for validation.

The 12 DSM-5 criteria for catatonia, and «malignant» symptoms (creatine kinase elevation, hyperthermia (at least 38.0°C), altered mental status, rigidity, hypertension, labile blood pressure, new-onset incontinence, diaphoresis, tachycardia and tachypnea[25] and other symptoms that influence prognosis: hypophagia[26], self-harm[27], altered sleep[28] were extracted. Two other descriptive features, seizure at presentation (associated with NMDARE[6]), and response to the benzodiazepine challenge test (potential diagnostic marker[29]) were also extracted. Final data coding was established by both raters, during a consensus meeting, for each variable independently and while blinding patient identification. The extraction and coding process achieved a 96,3% inter-rater agreement.

Data analysis

Our sample (Table 1) was stratified by sex and diagnostic threshold (“subthreshold” when less than 3 DSM-5 diagnostic criteria; “full DSM-5 diagnosis” when at least 3 criteria). Age distribution, median and interquartile range, sex-ratio (compared with the expected 1:1 ratio in the general population, using the exact binomial test), relative frequency (Fig. 2B) of each symptom as compared to the total count of symptoms with a same group (DSM-5, malignant and other symptoms) were reported. Analyses were performed separately within the subthreshold versus full DSM-5 diagnosis subgroups, and their concordance compared using Lin’s concordance correlation coefficient[30].

Table 1

Frequency of conditions co-occurring with catatonia in the sample, stratified by sex and diagnostic threshold for catatonia. For each condition, we compared the Male to Female ratio with the 1:1 ratio expected in the general population. M: Male, F: Female. Patients may have more than one co-occurring condition, so the total number of patients in each column exceeds the total number in the co-occurring condition row. Percentages indicate the ratio of individuals with each condition to the total number of individuals in their category (sex and diagnostic threshold). Among patients with NMDAR-antibody encephalitis, 19 patients (1 male and 18 females) had a psychotic disorder due to NMDAR-antibody encephalitis. Genetic diagnoses were trisomy 21 (n = 13), 22q11.2 deletion (n = 3), 7q11 duplication, Dravet syndrome, MECP2 deficiency, Phelan-McDermid Syndrome, Prader-Willi syndrome.

	M: n = 131		**F: n = 106**		**M:F ratio (p-value)**
Co-occurring conditions	**subthreshold n = 40**	**full DSM-5 diagnosis n = 91**	**subthreshold n = 38**	**full DSM-5 diagnosis n = 68**	**overall 1.236 (p = 0.0013)**
Neurodevelopmental disorders					
Overall (n = 76)	14 (35.0%)	34 (37.4%)	7 (18.4%)	21 (30.9%)	1.714 (p < 0.0001)
Autism Spectrum Disorder (n = 54)	11 (27.5%)	27 (29.7%)	3 (7.9%)	13 (19.1%)	2.375 (p < 0.0001)
Intellectual Disability (n = 44)	8 (20.0%)	14 (15.4%)	7 (18.4%)	15 (22.1%)	1.00 (p = 1)
Genetic diagnoses (n = 21)	4 (10.0%)	5 (5.5%)	4 (10.5%)	8 (11.8%)	0.75 (p = 0.1938)
Psychiatric disorders					
Overall (n = 104)	18 (45.0%)	46 (50.5%)	11 (28.9%)	29 (42.6%)	1.6 (p < 0.0001)
Psychotic disorder (n = 83)	14 (35.0%)	40 (44.0%)	7 (18.4%)	22 (32.4%)	1.862 (p < 0.0001)
Major depressive disorder (n = 23)	3 (7.5%)	9 (9.9%)	4 (10.5%)	7 (10.3%)	1.091 (p = 0.6832)
Bipolar disorder (n = 14)	4 (10.0%)	4 (4.4%)	2 (5.3%)	4 (5.9%)	1.333 (p = 0.2938)
NMDAR-antibody encephalitis (n = 41)	3 (7.5%)	6 (6.6%)	18 (47.4%)	14 (20.6%)	0.281 (p < 0.0001)

	M: n = 131		F: n = 106		M:F ratio (p-value)
Co-occurring conditions	**subthreshold** n = 40	**full DSM-5 diagnosis** n = 91	**subthreshold** n = 38	**full DSM-5 diagnosis** n = 68	**overall** 1.236 (p = 0.0013)
Neurodevelopmental disorders					
Unspecified catatonia (n = 92)	19 (47.5%)	39 (42.9%)	9 (23.7%)	25 (36.8%)	1.706 (p < 0.0001)

Within the subsample with catatonia not due to a general medical condition, we assessed tetrachoric correlation structure (Fig. 2C) among the 12 DSM-5 symptoms and ordered them using hierarchical clustering based on euclidean distance, using Ward's criterion[31]. We further reduced the dimensionality (Fig. 2D) of each of the two main clusters (we chose 2 clusters to obtain smooth dimensions) using Multiple Correspondence Analysis (MCA) with R package FactoMineR[32]. MCA is a dimensionality reduction (unsupervised learning) method that detects underlying relationships between symptoms. We summarized in the same way the 10 «malignant» symptoms into one dimension. These dimensions were fitted on the subsample of catatonia not due to a general medical condition and further predicted on the full sample, and then z-scored prior to regression analyses.

We modeled the associations (Fig. 3) between subtypes and conditions while accounting for all co-occurring conditions in all analyses. At the first level of analyses, we estimated the effects of broad groups of conditions: neurodevelopmental disorders, psychiatric disorders, and NMDAR-antibody encephalitis. At the second level of the analysis, we estimated the effects of the precise conditions included in these categories. By definition, unspecified catatonia occurred in the absence of other conditions, thus, we modeled its associations with symptoms and dimensions within a distinct model, i.e. without controlling for other conditions. The same model equations were also applied to estimate the association between conditions and each individual DSM-5 criteria and associated symptom as outcome, using a logit link function. Benjamini and Hochberg false-discovery rate (FDR) correction for multiple comparisons was applied to p-values, with respectively 30 (catatonia subtypes), 120 (precise DSM-5 symptoms) and 30 (other co-occurring symptoms) comparisons. Sensitivity analyses were used to control subthreshold versus full DSM-5 diagnosis catatonia, and covariates age and sex. We assessed the overall dependency (Fig. 4) of each sign on all conditions, age and sex, using Nagelkerke's r2, for which we obtained confidence intervals and p-values by bootstrap methods[33], 10,000 samples with replacement. We used a changepoint detection algorithm to find discontinuities across signs[34]. The significance threshold was fixed at $p < 0.05$, two-sided. Analyses were performed with R version 4.2.2.

RESULTS

Co-occurring conditions

184 records, related to 237 catatonic patients, satisfied inclusion criteria (Fig. 1, Supplement 2 and 3). 147 (61.2%) patients had co-occurring conditions: ND (76, 32.1%), psychiatric condition (104; 43.9%), NMDAR-antibody encephalitis (41, 17.3%), and 92 (38, 8%) "catatonia unspecified" did not have any of these conditions (Table 1).

Among the 76 patients with ND, 54 had ASD among which 27 had another ND, 18 were intellectually disabled or had a genetic diagnosis without ASD (see Supplement 4).

Among the104 patients with a psychiatric disorder not due to a general medical condition, 83 had a psychotic disorder, 23 had major depressive disorder, and 14 had bipolar disorder (Table 1). Seven of the 23 patients with a depressive disorder, and 9 of those with a bipolar disorder, also had psychotic features or history of a psychotic disorder, here thus labeled as an additional diagnosis of psychotic disorder (see supplement 4). A subset of patients (n = 25) had both a ND and a psychiatric disorder. In this subset, there were 17 patients with ASD, of which 13 had a psychotic disorder. 5 of the patients with ASD and a psychiatric diagnosis also had intellectual disability or a genetic diagnosis. 19 / 41 patients with NMDARE, also had a psychotic disorder attributable to the encephalitis (see supplement 4). Only 1.5% (3/196) of patients presented with seizures in catatonia not due to a general medical condition, as compared to 61% (25/41) in NMDARE. No patient had both a ND and NMDARE. 48% (40/87) of subjects that were administered a benzodiazepine challenge test showed improvement, and this was similar or even higher in subthreshold (53%, 9/17) than in full-diagnosis (44.3%, 31/70). However, only 1 out of 10 for the NMDARE group showed improvement when this test was administered.

Influence of co-occurring conditions on sex ratio and age distribution

The sex ratio was male biased with a maximal value of 2.375 M/ 1F in ASD, except for the NMDARE (0.281 M / 1 F) (Table 1). All conditions displayed a sustained increase of occurrence from age 14. The median age at diagnosis of catatonia was 15 years (25th centile: 14, 75th centile: 16) (Fig. 2A). There was no case before the age of 6 except in NMDARE. Median age at diagnosis of ASD among included patients was 3 years old (25th centile = 3, 75th centile = 5, data available for n = 21 patients). The time lapse median between ASD diagnosis and catatonia diagnosis for these patients was 11 years (25th centile = 9, 75th centile = 12).

Comparison of symptoms in subthreshold vs full-diagnosis catatonia (Fig. 2B)

The concordance frequency of symptoms in full diagnosis compared to subthreshold catatonia was 77.7% (95%CI: 61.1%, 87%), indicating few differences between the presentation of subthreshold and full diagnostic catatonia. All symptoms were similarly common in subthreshold and full-diagnosis catatonia, except mutism, which was more common in subthreshold catatonia (residual = 3.04 SD below other

symptoms), agitation, more common in subthreshold catatonia (residual = 2.31 SD below other symptoms), and waxy-flexibility which predominated in full-diagnosis (residual = 1.84 SD above other symptoms).

Catatonia symptom structure and subtypes

Two main clusters of catatonic symptoms emerged from the correlation and hierarchical clustering tree (Fig. 2C), each regrouping half of the symptoms. To represent different catatonia subtypes in a continuous dimension, we extracted a “retarded” subtype (Fig. 2D) that accounted for 30.51% or variance among the 6 signs of this cluster, and an “excited” subtype that accounted for 29.28% of variance among the 6 signs of this cluster. Stupor and waxy-flexibility were the symptoms with more weight in “retarded” catatonia, in comparison to stereotypy and echolalia in “excited” catatonia.

The “malignant” subtype, comprising all 10 malignant symptoms (Fig. 2E) accounted for nearly half (49.74%) of the variance of these signs. Diaphoresis, rigidity and urinary incontinence had a weak weight in “malignant” catatonia. There was a mild but significant correlation between the “excited” and “malignant” subtypes (r = 0.16, p = 0.012), suggesting an association between these subtypes[14]. There were no significant correlations between the “retarded” and “malignant” subtypes (r=-0.0092, p = 0.89), nor between the “excited” and “retarded” subtypes (r=-0.021, p = 0.74).

Differential effects of co-occurring conditions on catatonia subtypes (Fig. 3A**) and DSM-5 symptoms (**Fig. 3, B **and C)**

ND overall were associated with higher scores in the «excited» subtype (beta = 0.608, 95%CI: 0.416, 0.799), but not in the «retarded» and «malignant» subtype. Genetic diagnoses were associated with lower scores on the «malignant» subtype (beta=-0.26, 95%CI: -0.466, 0.054). Specifically, ND were associated with over-representation of agitation (OR = 2.06, 95%CI: 1.11, 3.83) and stereotypy, OR = 2.8 (95%CI: 1.46, 5.37), and under-representation of mutism (OR:0.50, 95%CI: 0.27, 0.96). In ASD catatonia, posturing (OR = 3.12, 95%CI: 1.01, 9.63) and grimacing (OR = 2.67, 95%CI: 1.01,7.02) were predominant, while in ID catatonia, posturing (OR = 0.26, 95%CI: 0.07, 0.97) was less present and agitation (OR = 3.29, 95%CI: 1.35, 8.02) more common.

Psychiatric disorders were associated with higher scores on “excited” (beta 0.261, 95%CI: (0.093, 0.429), “retarded” (beta 0.291, 95%CI :0.099, 0.483), and “malignant” (beta 0.367, 95%CI: 0.230, 0.505) subtypes. Bipolar disorder was also associated with higher scores on the «excited» subtypes (beta = 0.598, 95%CI: 0.238, 0.959) yet with lower scores on the «retarded» subtype (beta=-0.672, 95%CI: -1.025, -0.319). Psychotic disorders were associated with an over-representation of waxy-flexibility (OR = 2.83, 95%CI: 1.5, 5.32) and catalepsy (OR = 6,79, 95% CI = 1.29, 35.84). Major depressive disorder did not display any significant associations.

Unspecified catatonia was associated with lower scores in the “malignant” subtype (beta=-0,551, 95%CI: -0.687, -0.415) and specifically with an under-representation of agitation (OR = 0.2,95%CI: 0.1, 0.4).

NMDARE was associated with lower scores on the «retarded» subtype (beta=-0.592, 95%CI: -0.846, -0.339), yet higher scores on the “excited” (beta = 0.266, 95%CI: 0.047,0.485) and “malignant” subtypes (beta = 0.861, 95%CI: 0.632,1.090). Specifically, NMDARE was associated with an under-representation of posturing (OR = 0.18, 95%CI: 0.06, 0.51), and with an over-representation of agitation, (OR = 5.66, 95%CI: 2.56, 12.51).

As secondary outcomes, we examined other co-occurring symptoms. There were nominal associations between NMDARE and sleep disorder OR = 2.95 (95%CI: 1.43, 6.07), neurodevelopmental disorders and self-harm behaviour OR = 3.16 (95%CI: 1.22, 8.17), ASD and self-harm behaviour OR = 3.24 (95%CI: 1.06, 9.9). There was lower occurrence of hypophagia in both NMDARE, OR = 0.4 (95%CI: 0.18, 0.92) and neurodevelopmental disorders, OR = 0.4 (95%CI: 0.2, 0.8).

Influence of co-occurring conditions on catatonic symptoms

DSM-5 symptoms of catatonia were ranked from the most independent to the most dependent on co-occurring conditions (Fig. 4) and covariates (age, sex). The distribution of DSM-5 symptoms was discontinuous for mutism and negativism which displayed low dependency on co-occurring conditions ($p < 0.001$), while agitation, echopraxia and mannerisms displayed high dependency ($p = 0.002$).

DISCUSSION

Summary of findings

This systematic review of pediatric patients with catatonia provides the largest sample to date with symptom-level data. Analysing the relationship between co-occurring conditions and catatonia subtypes and symptoms improves the understanding of the epidemiology (sex-ratio and age of occurrence), semiology (variation of subtypes and symptoms according to the presence or nature of an associated condition) and the physiopathology of catatonia.

Relevance for the epidemiology of catatonia

Sex-ratio: The overall male-biased sex ratio of catatonia replicates previous findings[4]. Despite a modest sample size, it maps the sex ratio of each of the conditions with which it co-occurs. Critically, it is male-oriented in the ND and psychiatric conditions but is larger in Autism than in ID; In ID, the H:F sex ratio is known to be 1.6:1 in mild forms of ID but tends to normalize in severe forms or in the severe form (1.2:1)[10]. We did not replicate the male-biased ratio in ID, possibly due to a greater severity of ID in the present sample, or due to lack of power. The male-biased sex ratio was larger in Schizophrenia than in Major depressive disorder, and overall, larger in Autism than in Schizophrenia, which is congruent with ASD sex-ratio and to a lesser extent, Schizophrenia lifelong sex-ratio[35]. In contrast, the sex ratio is female-biased in NMDARE, as previously reported in this disorder that is sometimes associated with ovarian teratoma[6].

Age of occurrence

Catatonia is marked by a sharp increase following the age of 14 years old, independently of associated conditions such as ASD or ID. This supports previous observations based on a smaller number of cases[4,28]. When co-occurring with psychotic disorders, this peak could result from the peak age of diagnosis of this condition. However, this cannot be the case for ND diagnosed in childhood, nor for co-occurring psychiatric conditions in this population (as only 26,5% of our ASD sample developed psychiatric disorder). Catatonia develops in adolescence, regardless of the onset of its co-occurring conditions.

Relevance for detection and diagnosis of catatonia and comorbidities:

Clinical threshold. Sex ratio, age of occurrence and symptoms of subthreshold catatonia, largely overlap with those of full diagnosis catatonia, with some minor differences. Mutism being more common in subthreshold catatonia, the onset or exacerbation of mutism should lead to suspect subthreshold catatonia. This is clinically relevant, since the malignant symptoms are equally common in both conditions.

Clinical symptoms and subtypes: Two main clusters of catatonic symptoms emerged from the correlation and hierarchical clustering tree (Fig. 2C), each regrouping half of the symptoms. These clusters overlap with previous subdivisions of catatonia[5,11]. A subset of "retarded" symptoms - stupor, mutism, and negativism were least dependent on co-occurring conditions: These symptoms might be considered as prototypical symptoms of catatonia and may reflect a common denominator among all patients with catatonia, irrespective of their co-occurring conditions.

Symptoms of "excited" catatonia are present throughout the different neurodevelopmental and psychiatric disorders[4]. In NMDARE, in which cases excited subtypes[36], and mixed, excited and retarded subtypes[5] have been described, “excited" symptoms were overrepresented and retarded symptoms underrepresented. In BD, there were less “retarded” and more “excited” symptoms, like agitation, mimicking the expected symptoms of BD. “Malignant” form is more present in psychiatric and NMDARE, and less present in genetic disorders and unspecified catatonia, in which catatonia seems to be a less severe condition.

Given the symptom overlap between the different forms of catatonia and their co-occurring conditions[16], with certain symptoms occurring more frequently in some contexts than in others, granular observations of symptoms may result in optimizing the detection of catatonia or associated comorbidities. For instance, observing posturing and grimaces in a person with ASD, could also allow better detection of catatonia. As symptoms of catatonia in BD could mimic symptoms of BD, the appearance of stereotypies in a neurotypical patient could help distinguish symptoms of BD and catatonia. Waxy-flexibility, negativism, and catalepsy in a person with ASD might orient toward a comorbid psychosis, a diagnostic

challenge in non-verbal individuals. Conversely, some symptoms are highly dependent (mannerisms, echopraxia and agitation), and others are in between, orienting toward a differential weighting of signs according to the associated condition.

Relevance for underlying mechanisms of catatonia

A common mechanism could be involved in «malignant» catatonia and Neuroleptic Malignant Syndrome (NMS), such that exposure to neuroleptics precipitates these mechanisms[15,37,38]. Our study suggests however that malignant catatonia and NMS are clinically distinct, as fever, rigidity and mental status alteration are core symptoms in NMS[25,39], which is not the case in the present study. NMDARE causes autonomic nervous system dysfunction[6], increasing the NMS risk when exposed to neuroleptics[40]. Distinct "malignant" symptoms may share a pathophysiological pathway, but the extension of this mechanistic overlap remains unknown.

Lastly, about half of our patients without a medical condition responded to a benzodiazepine challenge test, whereas subthreshold patients displayed a slightly better response. This is congruent with the previously reported response rates of 40–50%[41], and with reports that non-responders had a higher count of catatonia symptoms[29]. However, only 1/10 of patients with NMDARE were responders, which is likely explained by the fact that NMDARE requires immunomodulation therapy.

Limitations

Publication bias could be present, either sampling bias (because our cohort is built on a systematic review of the literature, our sample might not be representative of the population), as well as observation bias (because symptoms were not consistently assessed). A prospective study would correct the first bias. The last bias is limited by the fact that the primary outcome of our study is based on DSM-5 criteria, a manual created to standardize diagnoses.

Conclusion

The diversity in subtypes and symptoms of catatonia reflects the broad scope of its co-occurring neurodevelopmental, psychiatric, and medical conditions. Our study confirmed the existence of subtypes of catatonia and strongly suggests that the malignant subtype is a clinical entity independent from NMS. We show that catatonia essentially develops during adolescence, regardless of the age of onset of co-occurring conditions, while its sex ratio still follows the sex ratio of co-occurring conditions. Some of catatonia defining features are dependent on co-occurring disease, while some are more less specific.Acknowledging this variability in the presentation of catatonia may allow the clinician both to better detect catatonia, or a hidden comorbid mental illness.

Declarations

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Contributions

All authors critically reviewed the report for important intellectual content and approved the final submitted version. All authors had full access to the data in the study and were responsible for the decision to submit for publication.

Role of the Funder/Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of interests

All authors declare no competing interests.

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Figures

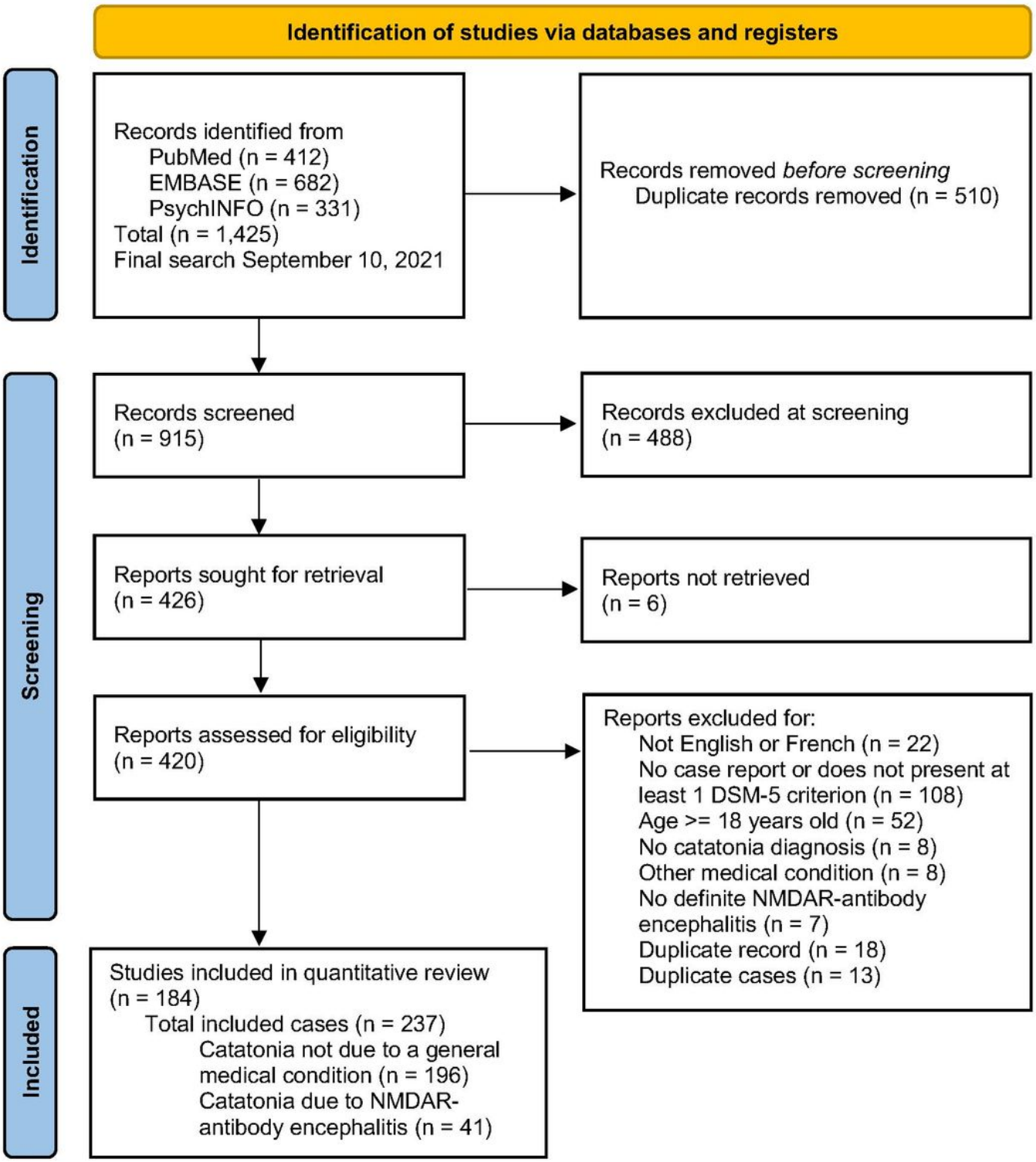

Figure 1

Flow diagram based on PRISMA statement (www.prisma-statement.org).

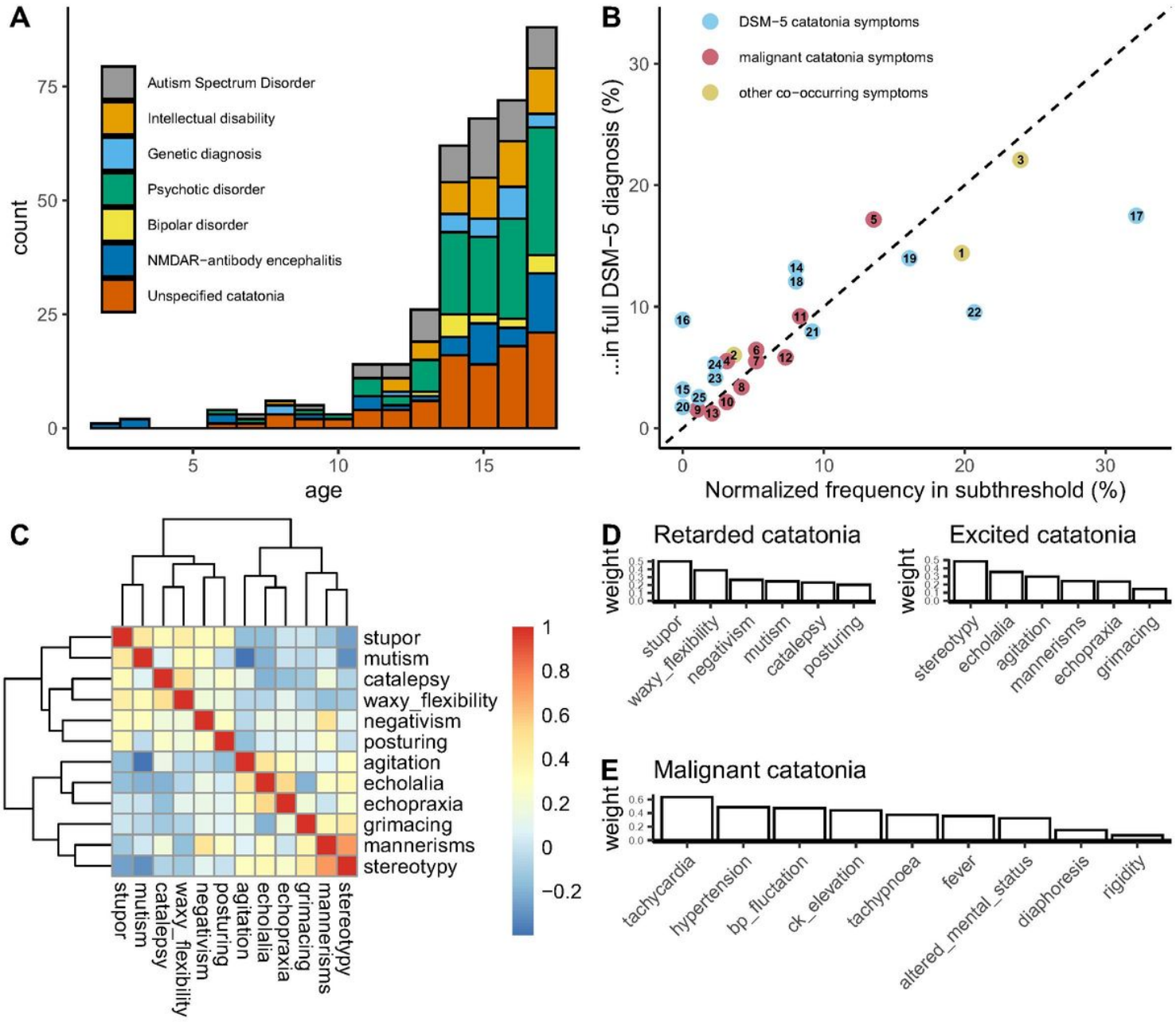

Figure 2

(A) Stacked distributions of co-occurring conditions as a function of age at presentation for catatonia.

(B) Concordance of the normalized frequency of symptoms in patients with subthreshold versus DSM-5 full-diagnosis catatonia.

Legend: 1-sleep_disorder, 2-self_harm_behavior, 3-hypophagia, 4-fever, 5-rigidity, 6-altered_mental_status, 7-ck_elevation, 8-hypertension, 9-bp_fluctation, 10-diaphoresis, 11-urinary_incontinence, 12-tachycardia, 13-tachypnoea, 14-stupor, 15-catalepsy, 16-waxy_flexibility, 17-mutism, 18-negativism, 19-posturing, 20-mannerisms, 21-stereotypy, 22-agitation, 23-grimacing, 24-echolalia, 25-echopraxia.

(C) Clustering of catatonia DSM-5 symptoms into two main subtypes, which correspond to «excited» and «retarded» catatonia.

(D) Weight of symptoms of «excited» and «retarded» catatonia, as measured by their correlation (r2) with these subtypes.

(E) Weight of symptoms of «malignant» catatonia, as measured by their correlation with this subtype. Urinary incontinence did not significantly weigh on the subtype and thus does not appear here. bp: blood pressure, ck: creatine kinase.

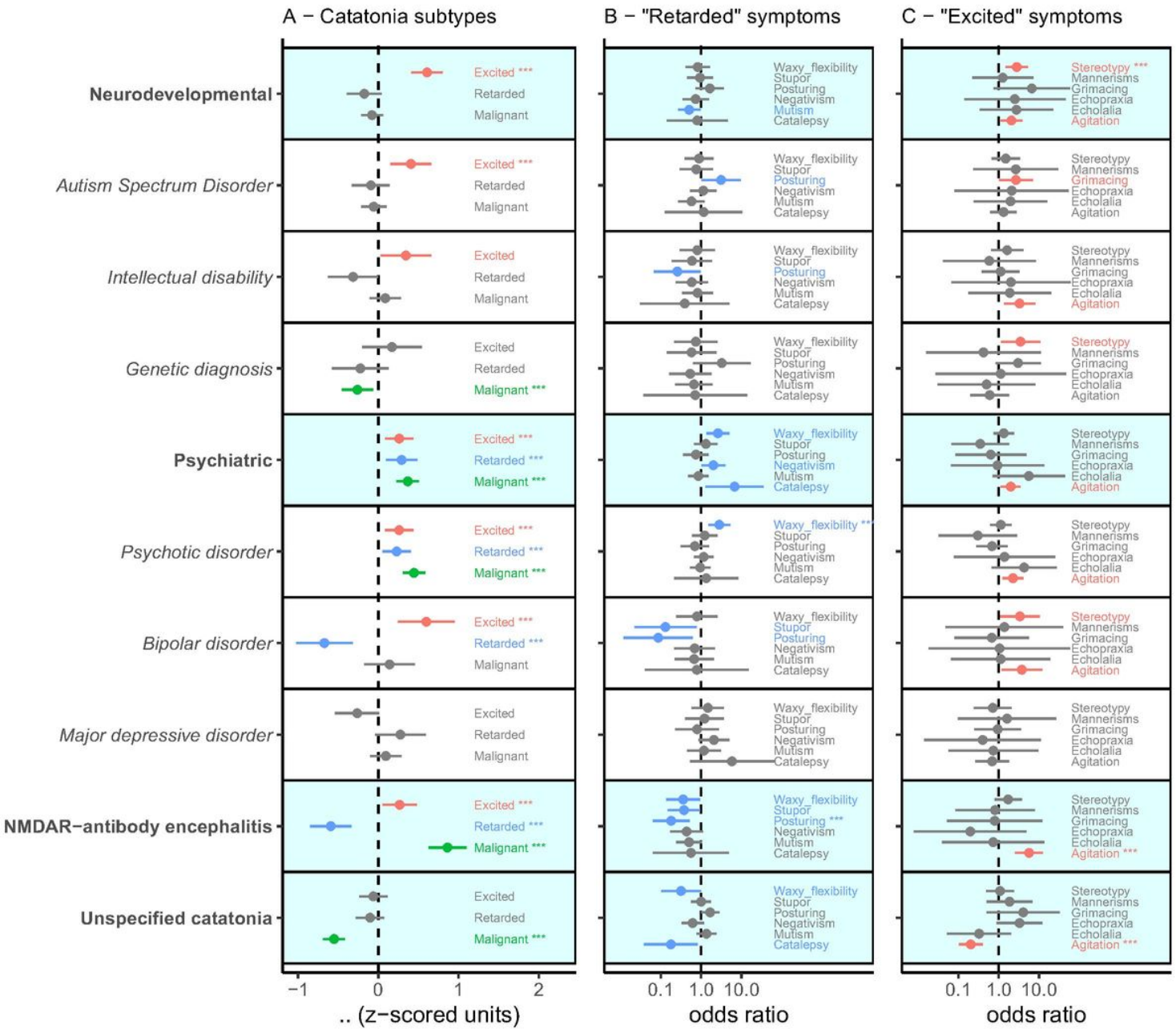

Figure 3

(A) Association of co-occurring conditions with “excited”, “retarded”, and “malignant” catatonia subtypes.

(B) Associations of co-occurring conditions with specific DSM-5 symptoms, classified into “retarded” and (C) “excited” catatonia symptoms.

Associations are estimated for both broader co-occurring conditions groups (bold), as well as specific co-occurring conditions (italics). Colored estimates and labels indicate nominal significance ($p<0.05$). Stars (***) indicate significance after Benjamini and Hochberg false-discovery rate (FDR) correction for multiple comparisons, FDR<0.05. Non-significant estimates are displayed in grey.

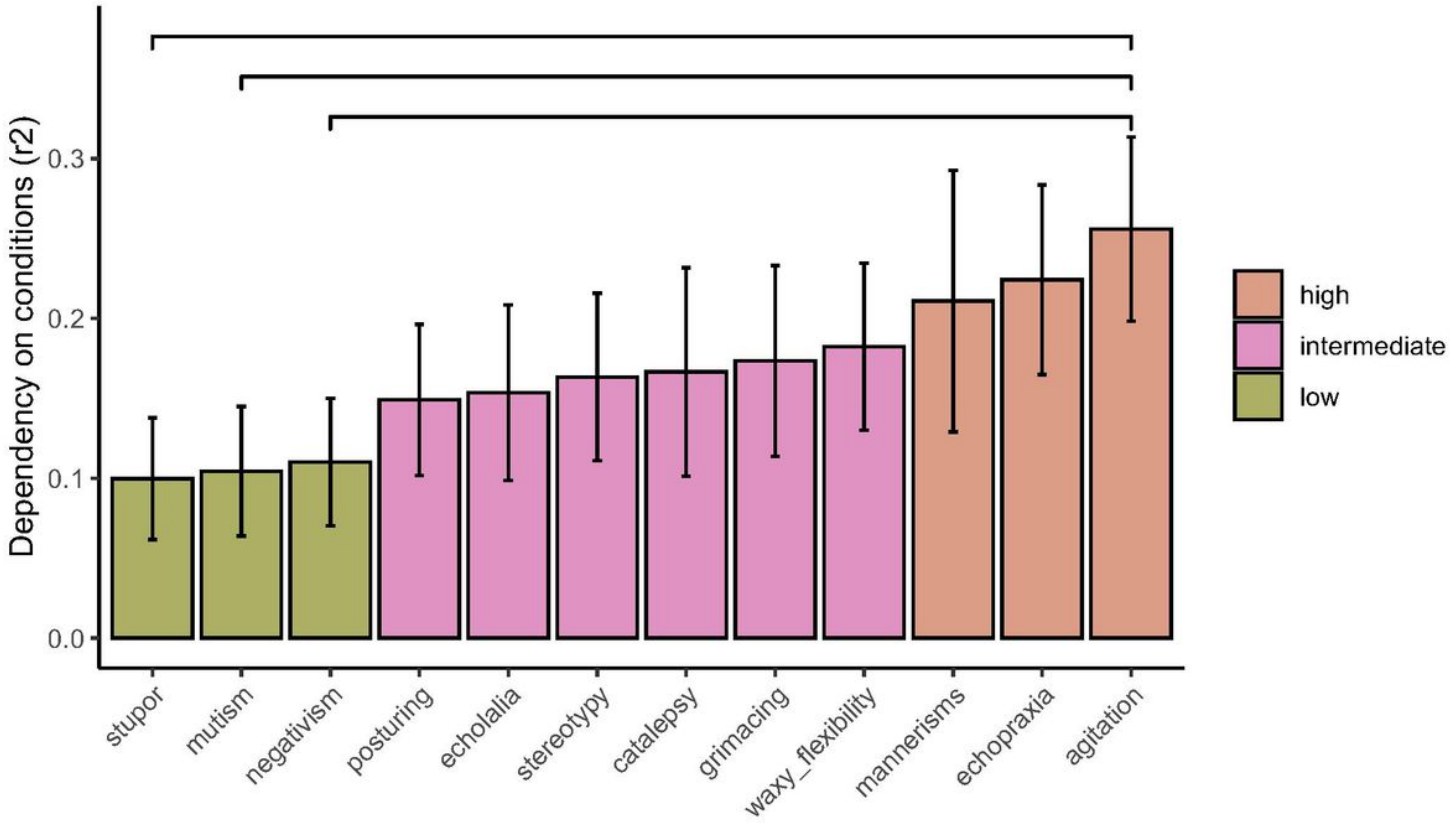

Figure 4

Ranking of DSM-5 symptoms from the least to the most dependent on all co-occurring conditions, age and sex. Error bars show the standard deviation. Brackets indicate significant differences ($p<0.05$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf
- Supplementarymaterialcatatonia.xlsx