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Concerns in reference to the paper, "Recognition and Management of Delirium in the Neonatal Intensive Care Unit: Case Series from a Single-Center Level IV Intensive Care Unit" by Dornette et al. published in J Child Neurol 2024 Apr 17:8830738241246693

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Dear Editor,

Members of the Johns Hopkins University School of Medicine - Neuroscience Intensive Care Nursery (NICN) Program and the University of California San Francisco – Departments of Neurology and Pediatrics would like to raise our concerns in reference to the paper, "Recognition and Management of Delirium in the Neonatal Intensive Care Unit: Case Series From a Single-Center Level IV Intensive Care Unit" by Dornette et al. published in J Child Neurol 2024 Apr 17:8830738241246693.[1] Our concerns are focused in the scientific premise, neurobiological assumptions, robustness of methods and validity of the conclusions.

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As the authors state, delirium is a cerebral dysfunction defined as an *acute neuropsychiatric disorder* with significant disturbances in attention, awareness, and cognition *without a previously diagnosed cognitive impairment*. The authors suggest that neonates are "untreated" due to lack of awareness about delirium as an entity, expertise in evaluating the behavioral symptoms and the non-distinctive delirium symptoms in neonates (e.g., disturbed consciousness, attention, wake-sleep cycles and thought processes). However, in the rapidly developing brain, frequently subject to the impact of comorbidities and our interventions, the identification of *an acute cerebral disorder* and the exclusion of a *cognitive impairment*, both essential diagnostic criteria of delirium, are challenging. In most cases, we do not have an established baseline of cognitive and behavioral function from which a change in function is discernable. Neither of these two essential diagnostic criteria have been specifically addressed and operationally defined in neonates by the authors in the manuscript. Perhaps because applying any DSM criteria and specifically the definition of delirium to the NICU population is quite complex. Particularly in premature infants, in whom many primary and secondary morbidities, including bronchopulmonary dysplasia, intraventricular hemorrhage and necrotizing enterocolitis, may adversely impact brain development, resulting in symptoms mimicking delirium, as characterized in older children and adults. Further, it is essential to recognize, that even premature infant without co-morbidities, develop difficulty with state regulation or motor manifestations that correspond to the described hyper and hypo active behaviors attributed to delirium. For instance as their developmental needs for social interaction increase and they remain mostly bound to their cribs, they may develop restlessness and agitation, which are further complicated by sedation strategies reversing their sleep/wake cycle. Therefore, evolving changes in general movement patterns may be mistaken for behaviors that are attributed to delirium in the older population.[2] Hence, neonatal neurologic tools which have been validated in this population should be used to appropriately assess orientation and state regulation.[3–5]

Beyond the definition of delirium in neonates, the neuroanatomical and biochemical substrates necessary for delirium may not exist during early brain development.[6,7] Delirium has been hypothesized as a "disconnection' syndrome caused by the loss of functional networks.[8–12] Thus, delirium, as defined in children and adults, requires functional neural pathways, synapses and biochemical & neurotransmitter networks involving many brain regions including the basal ganglia, thalamus, and cortex. In the preterm brain, even after reaching full-term corrected age, cholinergic, serotoninergic, glutamatergic, dopaminergic, and GABAergic systems are in a nascent stage of development as neurotransmitter levels do not peak until around age 2 to 10.[13] Specifically, brain levels of dopamine progressively increase until 1 year of age, serotonin until 1.5 years, acetylcholine until 4 years, and GABA until 10 years. Furthermore, individual neurotransmitter receptor subunits and second messengers also change dynamically until early adulthood. For instance, each NMDA receptor subunit has its own developmental trajectory, which peaks around 40 weeks gestational age in the brainstem and the basal ganglia, but not until 1 to 3 years of age in the cortex and 5 to 7 years of age in the hippocampus.[14–18] The rise of kainate and AMPA receptors follows that of NMDA, peaking after 4 years of age in the cortex and the hippocampus.[13,19–21] The connectivity of delirium-associated brain regions is also literally in its infancy at the age of the 9 participants included in this case series (median 50 weeks,

2.5 month corrected gestational age). For instance, connectivity between the cingulate and prefrontal cortex, which appears to be exquisitely linked to the emergence of delirium symptoms in elderly patients,[22–24] is still incipient until 10 years of age based on resting-state functional connectivity studies.[25] In summary, the structural and biochemical substrates are likely not sufficiently developed during infancy to make a diagnosis of delirium in neonates, even less in pre-term infants.

With the background presented above, we opine that the diagnostic tools for delirium used by the authors have not been robustly validated in the neonatal / infant population. Validation of a diagnostic tool requires a gold standard for comparison. Application of the DSM-5-TR criteria for delirium is fraught with difficulties in the neonatal population for the reasons mentioned. When neonatal delirium is poorly defined with no standardized diagnostic criteria, how can a diagnostic tool be rigorously validated? The Cornell Assessment of Pediatric Delirium (CAPD) scale has been used in children below 2 years of age, but has only been validated in the PICU population.[26,27] CAPD developmental anchors for the first 2 years of life attempt to correct the scale for neurodevelopment, but these anchors do not account for the many alternative neurodevelopmental trajectories encountered in the NICU. Additionally, most of the studies using the CAPD scale have included a strikingly low number of infants, and even lower of neonates.[26,28] The NICU cohort in this article does not include any neonates as the youngest patient is 10 weeks post-term corrected age. With respect to the use of the CAPD scale in growing premature infants in the NICU, any validation has yet to be performed. The CAPD scale does not account for various stages of myelination, immature neurotransmission and changes in connectivity with development, which are appropriately corrected for in the assessment and interpretation of other routine clinical diagnostics, such as imaging, EEG, and standardized neurodevelopmental examinations. Further, the CAPD is an observational screening tool. Screening tools are designed for use in a larger population to identify signs of a disorder that need further investigation using validated assessment, these screening tools are not appropriate for diagnosis independently. Therefore, In its current form, the CAPD scale does not meet the standard required for assessment of neonates and even less preterm infants.

Lastly, appropriate neurologic and developmental assessments and the return or progression to a developmentally appropriate environment in which these infants can thrive, should be the focus of our efforts as a scientific community, as aptly summarized in Figure I of the paper. Anti-psychotic medications such as quetiapine, olanzapine, risperidone and haloperidol, modulate the function of many of the neurotransmitters essential for brain development described above. Manipulation of the activity of these neurotransmitters and their receptors at this early stage of brain development could have unforeseen consequences and thus requires careful scrutiny and long-term follow up. In addition, these drugs have significant systemic effects on metabolism of lipids and glucose, which have not been studied in neonates. Pre-clinical and clinical data on these consequences and side effects are lacking. Therefore, we do not support the use of anti-psychotic medications in neonates, even less premature infants at any post-term corrected age, until robust pre-clinical and clinical data are available supporting their use. These medications and any effort made to study them must follow the utmost level of rigor to prevent unintended consequences in this very high-risk population.

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