2C-B AND NEURODIVERGENCE

A Case for Psychedelic-Assisted Therapy
in Autism and Related Conditions

Integrating the Karame Protocol:
A Four-Domain Framework for Compound-Assisted Trauma Resolution

Position Paper and Research Rationale

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Prefatory Note

This is a position paper and research rationale, not a clinical protocol or regulatory submission. It presents a hypothesis-generating framework for a novel research program. Where claims are mechanistic, they are identified as hypotheses. Where evidence is extrapolated from neurotypical populations, this is stated. The therapeutic model described herein (the Karame Protocol) is a conceptual framework requiring psychometric validation before clinical deployment. This paper has undergone two rounds of structured peer review and incorporates critiques from pharmacology, clinical trials methodology, autism research, bioethics, health economics, regulatory strategy, and science communications. The author uses "this paper" rather than "we" to reflect sole authorship at this stage; collaborative authorship is anticipated for future publications.

Abstract

Neurodivergent adults have been virtually excluded from psychedelic therapy research despite comprising an estimated 15–20% of the global population (Doyle, 2020). Autistic adults experience probable PTSD at 7–10 times the general population rate (Rumball et al., 2020; Haruvi-Lamdan et al., 2020), and approximately half meet criteria for alexithymia (Kinnaird et al., 2019)—a condition that impairs the emotional processing on which most therapies depend. Only one small pilot study (Danforth et al., 2018, MDMA, n=12) has tested any psychedelic intervention in this population.

This paper argues that 2C-B (2,5-dimethoxy-4-bromophenethylamine) warrants systematic investigation as a therapeutic adjunct for neurodivergent adults with treatment-resistant depression, anxiety, and post-traumatic stress. Controlled human data from Maastricht University (Mallaroni et al., 2023) and an ongoing multi-dose trial at the University of Basel (NCT05523401) suggest a pharmacological profile—mixed 5-HT2A/2C agonism, serotonin transporter interaction, maintained cognitive clarity, reduced dysphoria—that may be particularly suited to this population. This hypothesis has not been tested in any neurodivergent sample.

The paper also proposes the Karame Protocol, a four-domain integrative framework (Intellect–Emotion–Spirit–Body) with a three-tier dosing architecture (microdose maintenance, entactogenic session, psychedelic session) for neurodivergent-specific therapeutic scaffolding, and offers a historical reframing: that undiagnosed neurodivergence in mid-20th-century psychiatric populations may partly explain the efficacy observed in early psychedelic research with treatment-resistant patients.

Keywords: 2C-B, autism, neurodivergence, psychedelic-assisted therapy, alexithymia, rumination, trauma, serotonin, Karame Protocol, integrative framework

1. The Problem

1.1 A Population Excluded

The term neurodivergent encompasses autism spectrum conditions, ADHD, dyslexia, dyspraxia, dyscalculia, Tourette syndrome, and related neurodevelopmental profiles. The most widely cited

prevalence estimate—15–20% of the global population—derives from Doyle (2020, British Medical Bulletin), an aggregate of condition-specific prevalence data with inherent overlap. It is endorsed by the American Enterprise Institute (2024), Pearn Kandola (2024), and the City & Guilds Neurodiversity Index (2025, estimating 15% for the UK). A 2024 YouGov poll found 19% of Americans self-identify as neurodivergent. No single epidemiological study has measured neurodivergence as a unified category; the figure is used here as an informed estimate.

Despite constituting approximately one in five people, neurodivergent adults have been virtually excluded from the psychedelic therapy renaissance. The global evidence base consists of one completed trial: Danforth et al. (2018), MDMA-assisted therapy for social anxiety in 12 autistic adults. Several small-scale studies are now recruiting—Bedi's Australian MDMA trial (≈150 autistic adults), Lin's Toronto psilocybin study, McAlonan's King's College sensory-processing investigation—but all involve classical psychedelics or MDMA. No study of 2C-B in any neurodivergent population has been conducted, proposed, or registered.

This exclusion is structural. The dominant therapy models assume neurotypical processing: linear narrative, predictable emotional habituation, standard interoceptive feedback, conventional relational dynamics. As psychiatrist Hsiang-Yuan Lin observed (Science, 2024): "We cannot just say…the treatment response in a neurotypical brain will be the same as in an autistic brain."

1.2 Trauma Burden

Rumball et al. (2020, Autism Research) found approximately 60% of autistic adults reported probable lifetime PTSD versus 4.5% of the general population. Haruvi-Lamdan et al. (2020) reported 32% current probable PTSD versus 4% in controls. These rates reflect both higher exposure to interpersonal victimization (Guest & Ohrt, 2018; Im, 2016) and different processing: autistic individuals perceive events as traumatic that fall below DSM-5 Criterion A thresholds—sensory overwhelm, social confusion, routine disruption (Rumball et al., 2020; Kerns et al., 2022). Reduced cognitive flexibility, elevated rumination (Cooper et al., 2022; Gotham et al., 2014), and impaired suppression of unwanted thoughts create a processing environment in which trauma patterns persist despite sustained therapeutic effort.

A critical distinction: not all autistic distress is trauma-driven. Autistic burnout, sensory overload, and social exhaustion are direct consequences of environment-neurology mismatch, not post-traumatic responses. The present research program targets autistic adults with *documented trauma history and co-occurring treatment-resistant depression, anxiety, or PTSD*—not autistic distress broadly. Inclusion criteria must screen for trauma history, not merely symptom severity.

1.3 The Alexithymia Bottleneck

Alexithymia—difficulty identifying and describing emotional states, impaired interoception, externally oriented cognition—co-occurs with autism at a weighted mean prevalence of 49.93% versus 4.89% in neurotypical controls (Kinnaird et al., 2019, European Psychiatry). Estimates range from 40–65% (Bird & Cook, 2013) to 66% in clinical populations (Hobson et al., 2023).

Bird and Cook's alexithymia hypothesis (2013, Translational Psychiatry) proposes that emotional processing deficits attributed to autism are better explained by co-occurring alexithymia. This is influential but not settled: nearly 40% of autistic individuals do not meet alexithymia criteria

(Kinnaird et al., 2019), some studies identify autism-specific emotion processing differences independent of alexithymia (Oakley et al., 2016), and measurement instruments may function differently in autistic populations (Williams & Gotham, 2021). This paper adopts the hypothesis as a productive framework while acknowledging its evolving evidence base.

2. A Historical Reframing: The Undiagnosed Neurodivergent in Psychiatric History

This paper advances a historical hypothesis that recontextualizes the early psychedelic research era and its relevance to the present proposal.

Throughout the mid-20th century, psychiatric institutions housed large populations of treatment-resistant patients diagnosed with schizophrenia, personality disorders, and other conditions under the diagnostic frameworks available at the time. Autism was not a standalone diagnosis until DSM-III (1980). Asperger's syndrome was not added until DSM-IV (1994). ADHD did not appear in its current form until DSM-III (1980, as ADD). Prior to these classifications, individuals with neurodevelopmental conditions were routinely absorbed into existing diagnostic categories—most commonly schizophrenia, personality disorders, and "childhood psychosis"—or were institutionalized without specific diagnosis.

Given that neurodivergent conditions affect an estimated 15–20% of the general population, it is plausible that a substantial fraction—conservatively 10–30%—of institutionalized and treatment-resistant psychiatric patients in the 1950s through 1980s were undiagnosed neurodivergent individuals. Their social withdrawal, emotional dysregulation, sensory reactivity, communication differences, and resistance to conventional talk therapy were misattributed to psychotic or characterological pathology. Their trauma—which, as documented above, accumulates at dramatically elevated rates in neurodivergent populations—was unrecognized as trauma, because the processing differences that made them vulnerable to traumatization were themselves misread as symptoms of primary psychiatric illness.

Standard treatments failed these individuals not because the treatments were universally ineffective, but because they were treating the wrong condition. Talk therapy requires verbal emotional processing—the very capacity alexithymia impairs. Behavioral interventions require cognitive flexibility—the very capacity autistic processing constrains. Institutional environments, with their sensory unpredictability and social demands, replicated the conditions that produced the distress.

This reframing suggests a historical explanation for why early psychedelic research (1950s–1970s) showed striking results in treatment-resistant populations. The psychedelics—LSD, mescaline, and later MDMA and psilocybin—were reaching undiagnosed neurodivergent individuals whom conventional modalities could not reach. The compounds worked not despite the treatment resistance but because of its etiology: the resistance was neurodivergent processing architecture interacting with unresolved trauma, and psychedelics, by altering serotonergic function and increasing neural plasticity, may have temporarily bypassed the processing rigidity that held the trauma in place.

Sessa and Fischer (2015) documented underground MDMA-, LSD-, and 2C-B-assisted psychotherapy in Zurich spanning decades, with clinicians reporting that these compounds were most effective precisely in patients who had not responded to conventional treatment. While these reports are uncontrolled and retrospective, they are consistent with the hypothesis that psychedelic efficacy is partly driven by access to a neurodivergent subpopulation that conventional therapy cannot serve.

This historical hypothesis is unfalsifiable in its strongest form—we cannot retroactively diagnose mid-century asylum populations. It is offered not as a claim but as a reframing that generates testable predictions: if undiagnosed neurodivergence contributed to treatment resistance in historical psychedelic research populations, then contemporary studies that explicitly recruit neurodivergent participants should observe at least comparable, and potentially superior, therapeutic response rates. This prediction motivates the present research program.

2.1 Why 2C-B Among the Psychedelics

If the historical argument is correct—that psychedelics as a class reach neurodivergent processing where conventional therapy cannot—then the question becomes which compound is optimally suited for this population. This paper argues that 2C-B occupies a differentiated position among the serotonergic psychedelics for neurodivergent applications, based on comparative pharmacological and phenomenological considerations.

Versus MDMA: MDMA is the only psychedelic compound tested in autistic adults (Danforth et al., 2018). It showed efficacy for social anxiety. However, MDMA carries documented serotonergic neurotoxicity concerns with repeated dosing (Ricaurte et al., 2000; but see Mithoefer et al., 2019 for clinical safety data), produces significant cardiovascular stimulation, and its primary mechanism—massive serotonin release via SERT reversal—raises questions about sustained efficacy versus acute state change. 2C-B interacts with the SERT at lower potency (Liechti, NCT05523401 registration), potentially offering entactogenic warmth with reduced monoaminergic depletion risk.

Versus psilocybin: Psilocybin is the most clinically advanced psychedelic, with Breakthrough Therapy Designation and Phase 3 trials. Its primary mechanism—high-efficacy 5-HT2A agonism—produces profound alterations of consciousness including ego dissolution, which may be disorienting or distressing for individuals with alexithymia and sensory processing differences. Mallaroni et al. (2023) demonstrated that 2C-B at matched doses produced significantly less dysphoria, less subjective impairment, and lower ego dissolution than psilocybin.

Versus LSD: LSD's 8–12 hour duration is a significant practical and tolerability concern for a population with heightened sensory sensitivity. Its potent 5-HT2A agonism and broad receptor profile produce an intense and prolonged altered state that may exceed the therapeutic window for many neurodivergent individuals.

Versus ketamine: Ketamine (and its enantiomer esketamine, FDA-approved as Spravato for TRD) operates through NMDA receptor antagonism rather than serotonergic mechanisms, producing dissociative rather than psychedelic effects. While it has shown rapid antidepressant effects, its mechanism does not address the serotonergic and social-emotional processing dimensions that are central to the neurodivergent trauma hypothesis.

None of these comparisons constitute evidence that 2C-B is superior. They constitute a rationale for investigation based on pharmacological profile matching to clinical need. Comparative efficacy is an empirical question that can only be answered by clinical trials.

3. The Compound: 2C-B

3.1 Pharmacological Profile

2C-B is a synthetic phenethylamine first synthesized by Alexander Shulgin in 1974 (PiHKAL, 1991) for psychotherapeutic use. It was scheduled in the U.S. in 1995 and internationally in 2001.

2C-B's receptor pharmacology is distinctive but incompletely characterized. In vitro data shows low-efficacy 5-HT2A partial agonism in functional selectivity assays (Moya et al., 2007, JPET) and functional antagonism in Xenopus laevis oocyte expression systems (Villalobos et al., 2004, BJP). These findings are not contradictory but reflect different assay systems, cell types, and species—a discrepancy that underscores the incompleteness of 2C-B's in vitro characterization and the difficulty of extrapolating from receptor-level data to human pharmacodynamics. Rickli et al. (2016, European Neuropsychopharmacology) provided quantitative binding affinities for 2C-B across 5-HT2A, 5-HT2B, and 5-HT2C receptors, confirming meaningful activity at all three subtypes with a profile distinct from classical tryptamine psychedelics.

The Liechti laboratory's trial registration (NCT05523401) notes that 2C-B also interacts with the serotonin transporter (SERT), similar to MDMA but at lower potency. This dual receptor agonism plus transporter interaction is consistent with 2C-B's reported mixed entactogenic-psychedelic profile and distinguishes it pharmacologically from both pure 5-HT2A agonists (psilocybin, LSD) and pure SERT releasers (MDMA).

Essential caveat: In vitro pharmacology does not predict in vivo human experience with precision. Biased agonism at the 5-HT2A receptor—differential activation of Gq versus β-arrestin pathways—modulates whether a compound produces psychedelic-like effects, neuroplasticity, or both (Jastrzębski et al., 2025; Kaplan et al., 2022). 2C-B's biased agonism profile has not been fully characterized. The pharmacological rationale presented here is hypothesis-generating, not mechanistically conclusive.

3.2 Controlled Human Data

Two laboratories have conducted or registered controlled human studies with 2C-B:

Maastricht University (Ramaekers & Mallaroni)

Mallaroni et al. (2023, Clinical Pharmacology & Therapeutics): double-blind, placebo-controlled crossover of 2C-B (20 mg), psilocybin (15 mg), and placebo in 22 healthy adults. Key findings: 2C-B produced psychedelic alterations with significantly less dysphoria, subjective impairment, and ego dissolution than psilocybin. Doss et al. (2024): both compounds distorted episodic familiarity via a common neurocognitive mechanism. Mallaroni et al. (2026, Molecular Psychiatry): 7T fMRI confirmed distinct brain reorganization patterns. Mallaroni et al. (2022, Psychopharmacology) additionally mapped the experiential fingerprints of novel psychedelics including 2C-B in recreational user populations, providing phenomenological context.

University of Basel (Liechti)

NCT05523401: Phase 1 randomized, double-blind, placebo-controlled, five-way crossover comparing 2C-B at 10, 20, and 30 mg with MDMA (125 mg) and psilocybin (25 mg) in healthy volunteers. This will provide the first controlled multi-dose characterization and the first direct within-subjects 2C-B/MDMA/psilocybin comparison. Results anticipated 2025–2026. The 10 mg dose data is directly relevant to the entactogenic range hypothesized as therapeutic for neurodivergent populations.

Observational and Underground Clinical Data

Papaseit et al. (2018, Frontiers in Pharmacology): observational study in recreational users (not controlled). Sessa & Fischer (2015): documented underground 2C-B-assisted psychotherapy in Zurich over multiple decades, with clinician reports of efficacy in treatment-resistant patients. While uncontrolled and retrospective, this represents the only published record of 2C-B's use in an actual therapeutic context.

What this data does not tell us: No controlled data exists in autistic participants, psychedelic-naive participants, clinical populations, or in combination with any structured therapeutic protocol. These are the gaps the proposed research program addresses. This paper will adaptively incorporate results from the Basel trial as they become available; if 10 mg proves subtherapeutic or 30 mg produces unacceptable adverse events, the dose strategy will be revised accordingly.

3.3 Why 2C-B for Neurodivergent Populations

The following features align with hypothesized clinical needs. Each requires validation in the target population:

Maintained cognitive clarity. Less subjective impairment than psilocybin at matched doses (Mallaroni et al., 2023). Autistic individuals who rely on cognitive control as a primary regulatory strategy may better tolerate a compound that permits emotional access without cognitive dissolution.

Reduced ego dissolution. Lower ego dissolution scores suggest boundary-softening without collapse—potentially more tolerable for alexithymic individuals.

Mixed entactogenic-psychedelic profile. Dual 5-HT2A/2C agonism plus SERT interaction produces emotional warmth alongside perceptual shift. The entactogenic component targets empathic and social difficulties directly.

Shorter duration. 4–6 hours versus 4–8 (psilocybin) or 8–12 (LSD). Reduced exposure for sensory-sensitive populations.

Dose-dependent spectrum. Anecdotal gradient from entactogenic (5–10 mg) to psychedelic (25+ mg). Basel trial will provide the first controlled characterization of this gradient.

4. The Karame Protocol

4.1 Philosophical Foundations

The Karame Protocol assesses the whole person across four domains: **Intellect** (cognitive processing, executive function, metacognition); **Emotion** (affective regulation, empathy, social cognition, interoception); **Spirit** (meaning-making, purpose, existential coherence—secular, not religious); and **Body** (somatic awareness, sensory processing, physiological regulation). This architecture traces to Aristotle's De Anima (nutritive/sensitive/rational soul), through Aquinas's fourfold causality, to contemporary recoveries in somatic psychology (van der Kolk, Levine), developmental theory (Piaget, Maslow), and contemplative neuroscience (Vago & Silbersweig).

4.2 Validation Status

The Karame Four-Domain Assessment (K4DA) is a conceptual framework drawing on validated sub-instruments—TAS-20 and DERS (Emotion), neuropsychological batteries (Intellect), Meaning in Life Questionnaire (Spirit), Adolescent/Adult Sensory Profile (Body)—but has not itself been operationalized, normed, or psychometrically validated. Required before clinical use: operationalized scoring, inter-rater and test-retest reliability, convergent and discriminant validity, and normative data in autistic and neurotypical adult populations ($n \geq 100$ per group). Validation is Phase 0 of the research agenda.

4.3 Three-Tier Dosing Architecture

The Karame Protocol employs a three-tier dosing architecture that leverages 2C-B's dose-dependent spectrum in a way no other compound in the current pharmacopoeia permits with the same granularity and tolerability:

Tier 1 — Microdose Maintenance (1–3 mg, sub-perceptual). Administered on a defined schedule (e.g., every third day) between macro-dose sessions. Maintains low-level serotonergic modulation and baseline inter-domain accessibility during integration periods. Hypothesized to sustain enough neurochemical flexibility for integration work without producing perceptible altered states. No controlled 2C-B microdosing data exists; characterization is included in Phase 1 as an exploratory arm.

Tier 2 — Entactogenic Session (10–15 mg). The primary therapeutic dose. Emotional warmth, maintained cognitive clarity, boundary softening without dissolution. This is the core of the Karame Protocol — pharmacologically facilitated access to the body-emotion loop where neurodivergent trauma is encoded, with sufficient cognitive structure preserved for the individual to participate in their own integration. Four-domain guided therapeutic work occurs within the therapist dyad during this session.

Tier 3 — Psychedelic Session (20–25 mg). Reserved for participants demonstrating readiness after Tier 2, whose therapeutic process indicates deeper processing is needed and whose Tier 2 response data supports escalation. Not mandatory. Not first-line. Dose escalation is a collaborative clinical decision informed by Tier 2 response data and ongoing K4DA assessment.

This three-tier architecture respects sensory sensitivity and cognitive rigidity by not beginning at full psychedelic intensity, provides pharmacological continuity between sessions via the microdose maintenance tier, and creates a structured escalation pathway that is individually titrated rather than protocol-mandated.

4.4 Clinical Application

Assessment: K4DA four-domain evaluation. Alexithymia screening mandatory (TAS-20). Sensory profiling (Adolescent/Adult Sensory Profile) informs environment design. *Trauma history screening is an inclusion criterion*, distinguishing trauma-driven distress from environment-driven autistic distress.

Preparation: Sensory environment customization based on individual sensory profile, regulatory tools, pre-established non-verbal communication protocols, psychoeducation in the individual's preferred modality using the four-domain model as a scaffolding framework.

Dosing session: Therapist dyad with at least one neurodivergent-affirming clinician. Dosing begins at Tier 2 (entactogenic) for all participants. Four-domain guided therapeutic work during the session. Whether directive four-domain guidance or non-directive support (Richards, 2015) produces better outcomes in this population is an open empirical question to be explored qualitatively in Phase 2.

Integration: Structured four-domain review following each session. Tier 1 microdose maintenance between sessions. Consistent K4DA framework for inter-session therapeutic work, allowing clinician and participant to track movement across domains over the course of treatment.

4.5 Participatory Design

The autism research community has moved firmly toward participatory methodology. This paper is authored by a non-autistic founder; future protocol development will involve an autistic advisory panel convened during Phase 0, with autistic adults contributing to assessment design, session environment specifications, consent methodology, and outcome measure selection. The Cedar Institute commits to the principle that research concerning neurodivergent populations should involve neurodivergent people in its design.

5. Exclusion Criteria, Informed Consent, and Safety

5.1 Exclusion Criteria

Psychotic spectrum: Personal or first-degree family history. **Epilepsy:** Active seizure disorder (prevalence 12–26% in autism; 2C-B's seizure threshold interaction unknown). **Serotonergic medications:** Current SSRI/SNRI use requires supervised tapering and washout. **Intellectual disability:** Protocol requires informed consent capacity and self-report. **Cardiovascular:** Uncontrolled hypertension, arrhythmia, significant disease. **Active suicidality:** Ideation with intent or plan. **Pregnancy/breastfeeding. No documented trauma history:** This protocol targets trauma-driven distress specifically.

5.2 Informed Consent for Alexithymic Populations

When approximately half the target population has difficulty identifying their emotional states, standard consent faces a fundamental challenge. Proposed adaptations: extended multi-session consent timeline using preferred communication modalities; multi-modal materials (written, plain-

language, visual, audio); experiential familiarization session in the therapeutic setting without the compound; pre-established non-verbal withdrawal signals with consent treated as continuous; and supported decision-making with a trusted person (not proxy consent).

5.3 Safety Monitoring

All phases will operate under independent Data Safety Monitoring Board (DSMB) oversight. Cardiovascular monitoring during dosing sessions. Post-session follow-up adequate for delayed adverse events. The DSMB will have authority to halt or modify the protocol based on emerging safety signals, including any relevant findings from the Basel trial.

6. Clinical Outcomes

Primary outcomes: PTSD symptom reduction (PCL-5), depression severity (MADRS), anxiety (GAD-7), alexithymia (TAS-20), quality of life (WHOQOL-BREF). These justify the intervention on ethical and regulatory grounds. The intervention is justified by suffering and the right to effective treatment, not by economic productivity or cognitive enhancement.

It remains a secondary, testable hypothesis that reduced trauma-processing burden may liberate cognitive and perceptual resources, and that the distinctive architecture of neurodivergent cognition may produce differentiated contributions when not running defensive subroutines. This is an observation, not the clinical justification.

7. Research Agenda

Phase 0: Instrument Development (12–18 months)

Psychometric validation of the K4DA. Operationalized scoring, reliability testing, convergent validity, normative data ($n \geq 100$ per group). Publication required before clinical deployment. Autistic advisory panel convened.

Phase 1: Pilot Characterization (18–24 months)

Controlled pilot comparing acute effects of 2C-B (20 mg, matching existing Maastricht data) in autistic (n=25–30) versus neurotypical (n=25–30) healthy volunteers, using 7T fMRI, validated subjective experience measures, K4DA, and cardiovascular monitoring. Exploratory microdose arm (2 mg) to begin characterizing Tier 1 parameters. Single-dose design maximizes statistical power for the primary between-groups comparison. Dose may be adjusted to 10 mg pending Basel results. Primary outcome: differential functional connectivity patterns. Secondary: safety, tolerability, subjective experience differences. Leverages existing Maastricht infrastructure and Dutch regulatory approvals. DSMB oversight from first participant.

Phase 2: Protocol Pilot (24–36 months)

Open-label pilot of the full Karame Protocol — three-tier dosing architecture — in 16–20 autistic adults with documented trauma history and treatment-resistant depression/anxiety. Tier 1

microdose maintenance between sessions, Tier 2 entactogenic sessions as primary therapeutic intervention, Tier 3 psychedelic sessions for participants demonstrating readiness. Outcomes at baseline, post-treatment, 3-month, and 6-month follow-up. Qualitative exploration of directive versus non-directive therapeutic approaches via clinician observation and participant self-report—not a formal comparison (insufficient power). DSMB oversight.

Phase 3: Controlled Efficacy

Randomized, double-blind trial versus active placebo (very-low-dose 2C-B or niacin) with matched therapeutic support. Sample size powered by Phase 2 effect sizes. Expectancy measurement and post-trial blinding assessment address functional unblinding. DSMB oversight.

Regulatory Pathway

2C-B has no IND history at FDA. No U.S. institution holds a DEA Schedule I Researcher Registration for the compound. The practical regulatory pathway is untested.

Recommended strategy: begin internationally. Maastricht holds Dutch permits for 2C-B. Basel operates under Swiss authorization. The Dutch government's 2024 establishment of an independent state commission evaluating MDMA's therapeutic potential signals growing institutional openness.

For U.S.-based research: (1) FDA Type B Pre-IND meeting to discuss novel compound, novel indication, and novel therapeutic framework; (2) IND application supported by international data; (3) DEA Schedule I Researcher Registration (6–12 months additional). DEA's published 2C-B production quota (5,100g, 91 FR 287) confirms the compound exists within the regulatory framework. Realistic timeline to NDA-ready data: 8–12 years.

Indicative Cost Framework

Phase 0 (K4DA validation): estimated €100K–€200K (primarily staff time, assessment administration, and data analysis). Phase 1 (pilot characterization at Maastricht, single dose, n=50–60 total, 7T fMRI): estimated €800K–€1.5M, comprising participant screening and medical workup, compound procurement and pharmacy, MRI scanning time, psychometric administration, data analysis, and publication. Phase 2 (protocol pilot, n=16–20, two sessions per participant, three-tier dosing): estimated €500K–€1M, comprising therapist training, clinical space, compound procurement, medical monitoring, follow-up assessments, and analysis. Total estimated funding need through Phase 2 go/no-go decision: €1.4M–€2.7M. This follows the Beckley Foundation model: fund the delta—the cost of extending an existing laboratory's capability to a new population and research question—rather than building infrastructure.

8. Limitations

1. n=0 in the target population. No study of 2C-B has included neurodivergent participants. The pharmacological rationale is extrapolated from neurotypical data. Autistic neurobiology differs in receptor density, functional connectivity, sensory gating, and neurotransmitter metabolism.

2. The Karame Protocol is unvalidated. The K4DA is conceptual, not operational.

3. The inter-domain permeability hypothesis is speculative. It layers philosophical taxonomy onto neuroimaging data without direct empirical support.

4. The entactogenic dose range is incompletely characterized. Controlled 10 mg data is anticipated from Basel but not yet published.

5. The historical reframing is unfalsifiable. We cannot retroactively diagnose mid-century psychiatric populations. It is offered as a hypothesis that generates testable predictions.

6. The alexithymia hypothesis is evolving. Evidence is substantial but not unanimous.

7. In vitro pharmacology is inconsistent. Moya (2007) and Villalobos (2004) report different functional profiles (partial agonism vs. antagonism) across different assay systems. The functional pharmacology at human 5-HT2A in vivo is unresolved.

8. Founder conflict of interest. The founder has personal experience with 2C-B. The program includes independent scientific oversight, pre-registered protocols, DSMB, and independent data monitoring. The foundation funds; the university conducts.

9. Regulatory uncertainty. Zero IND history, no U.S. DEA registration, untested practical pathway.

10. No autistic co-authorship at this stage. This paper is authored by a non-autistic founder. Autistic advisory involvement is committed for Phase 0 onward.

These limitations define the research program. Every gap is addressable through the phased agenda. Honest naming of what is unknown is the prerequisite for studies that produce knowledge.

9. Ethical Framework

Neurodiversity-affirming: Different, not deficient. Liberation from trauma interference, not normalization. Outcomes defined by the participant.

Informed consent: Adapted for alexithymic populations (Section 5.2).

Safety: DSMB oversight at all phases. Exclusion criteria rigorously applied. Cardiovascular monitoring.

Spiritual domain: Secular meaning-making assessment. No religious framework or expectation.

Participatory: Autistic advisory panel from Phase 0. Nothing about us without us.

Publication: Pre-registered protocols. Results published regardless of outcome.

10. Conclusion

The case rests on three empirically testable pillars. First: that 2C-B's pharmacological profile makes it a differentiated candidate for neurodivergent populations. Second: that the Karame

Protocol provides a clinically useful framework for neurodivergent trauma therapy. Third: that the combination outperforms either component alone. Each requires validation through the phased research agenda.

A fourth, historical hypothesis offers additional motivation: that undiagnosed neurodivergence in mid-20th-century psychiatric populations partly explains the efficacy observed in early psychedelic research with treatment-resistant patients, and that explicitly recruiting neurodivergent participants in contemporary studies will confirm this pattern.

What is not hypothesis is the need. Autistic adults experience PTSD at 7–10 times the general population rate. Half carry alexithymia. Conventional treatments leave many cycling through therapies that provide insight without resolution. The psychedelic therapy renaissance has nearly ignored them. One completed trial (n=12) does not constitute adequate attention to 15–20% of humanity.

Whether 2C-B is the right compound, the Karame Protocol the right framework, and the combination the right therapy—these are empirical questions. This paper names them with precision sufficient to permit investigation.

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