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Towards a Strengthened Addictions Neuroclinical Assessment (ANA) Framework: A Perspective on Current Assessment Approaches and The Added Value of Recovery-Inspired Dimensions

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Introduction

Alcohol is the most widely used, socially valorized, and yet harmful drug in the world, being the third most frequent cause of preventable death, as three million deaths per year are attributed to alcohol (Mellinger, 2019; Singal & Anand, 2013; Witkiewitz et al., 2019). In the United States, the estimated lifetime prevalence of alcohol use disorder (AUD) is 29.1%. Amongst patients with AUD, 13.9% present with DSM-5 criteria of severe AUD (SAUD) (Grant et al., 2015). However, with a treatment gap of approximately 80%, access to care remains markedly lower in SAUD than in other psychiatric disorders (Grant et al., 2015; Kohn et al., 2004; Mekonen et al., 2021; Venegas et al., 2021). Among the patients who initiate abstinence through in- or out-patient care, more than 75% relapse within the months following detoxification (Moos & Moos, 2006). In the long run, around 50% of patients with AUD achieve remission (Fleury et al., 2016), showing the yet limited efficacy of the current treatments (Campbell et al., 2018). For patients with SAUD who do reach care, there is thus an urgent need to develop interventions that significantly improve outcomes in this chronic and relapsing condition, by focusing on a better understanding of individual relapse factors and by integrating biological, psychological, and social dimensions. Hitherto, the various factors predicting relapse have mostly been explored independently, which has hampered the identification of their respective weights and interactions, and the formulation of personalised clinical guidelines (for review, see (Sliedrecht et al., 2019)).

The Addictions Neuroclinical Assessment (ANA) has been proposed as a clinical framework to operationalise in clinical research the Alcohol and Addiction Research Domain Criteria (AARDoC), an emerging dimensional approach centred on neuroscience (Litten et al., 2015) and inspired by the Research Domain Criteria (RDoC) (Casey et al., 2013; Cuthbert & Insel, 2013). This novel approach offers a more precise characterisation of patient heterogeneity than the clinical

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classification outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), promising to provide guidance on individualised care (Cuthbert & Insel, 2013; Insel et al., 2010). However, the ANA remains essentially centred on brain-related and cognitive processes. It hence fails to adequately account for key psychosocial factors that are critical to daily clinical care and to a comprehensive understanding of each patient's lived experience in a recovery perspective. Integrating those psychosocial aspects (Akram & Giordano, 2017; Dean, 2019), developing concrete clinical propositions based on neuroscientific models (Luk & Thompson, 2024; Rezapour et al., 2025) and promoting integration of those models into the clinical settings (Williams et al., 2024) are essential for these approaches to have a real clinical impact, beyond the research field.

In this perspective paper, we will first briefly revisit the conceptual emergence of the ANA model. Secondly, we present the three established ANA domains with their validated assessment tools, as well as the faced challenges and perspectives to consolidate the actual ANA model. We then examine how recovery-informed concepts may strengthen the ANA framework and open to a more comprehensive model by proposing the addition of a fourth domain and by highlighting previously overlooked dimensions. We consider this essential for improving the model in order to enhance the understanding of individual trajectories and the clinical integration. Finally, we open on the therapeutical perspectives resulting from this approach.

A promising new approach

In 2008, the National Institute of Mental Health (NIMH, USA) proposed a new framework for psychiatric research with the Research Domain Criteria (RDoC) initiative, applying an integrated knowledge of cognitive-behavioural neurosciences, brain circuits, and genetics to develop

precision medicine (Cuthbert, 2014; Cuthbert & Insel, 2013; Insel et al., 2010). Addiction was not initially included but in 2015, Litten initiated the AARDoC, building upon Koob's addiction cycle, an established translational bio-psychological model (Koob, 2013; Koob & Moal, 1997; Litten et al., 2015). It aims to improve the understanding and prediction of individual clinical trajectories in the addiction field. This soon led to development of a *clinical* battery, the ANA (Kwako et al., 2016), which focusses on three key functional domains – incentive salience (IS), negative emotionality (NE), and executive function (EF) – linked to the three phases of the addiction cycle – binge-intoxication, withdrawal-negative affect, and preoccupation-anticipation, respectively – and thus relates to specific functional cognitive processes and neurocircuit targets (Koob, 2013; Kwako et al., 2016). The ANA domains have been studied across different AUD populations (healthy volunteers (Kwako et al., 2019), non- help-seeking (Votaw et al., 2023) and help-seeking patients (Kirsch et al., 2024; Votaw et al., 2020), heavy drinkers patients (DeMartini et al., 2021) and AUD (Stein et al., 2021)), and methamphetamine users (Nieto & Ray, 2022) and have been related to relapse risk (Linn et al., 2023; Stein et al., 2021; Votaw et al., 2021; Witkiewitz et al., 2023). In the literature, there is an increasing emphasis on comprehensive, patient-centred approaches to better understand relapse (Dacosta-Sánchez et al., 2021) and the ANA model precisely allows for the investigation of patients' phenotypes based on a neurobehavioral model (e.g., differential patterns of deficits across IS, EN or EF domains) (Kwako et al., 2018). It can thus provide a "neurobehavioral profile" (e.g., impaired IS but preserved EN/EF) and open the way for future individually tailored interventions. A promising avenue consists in leveraging neurobiological and neurobehavioral frameworks to identify more homogeneous patient subgroups and advance precision medicine approaches in addiction. This approach moves beyond the symptom-based therapeutic model by rather targeting its underlying mechanisms.

The 3 ANA domains

Building on the three phases of the addiction cycle, Kwako and colleagues proposed a framework that organizes the underlying mechanisms of addiction into three domains: IS, NE, EF (Kwako et al., 2016). In the original paper, self-report questionnaires, behavioral tasks and brain imaging were proposed to assess these domains, consistent with the neurobiological orientation of the ANA framework. In practice, however, most studies on ANA have attempted to capture its three domains using factor-analytic approaches, mainly relying on questionnaire data (Table 1) and, less commonly, on behavioral tasks (Folker et al., 2024; Gunawan et al., 2024; Nieto et al., 2021) (Supplemental Table A). We therefore review these domains and the assessment approaches that have been mostly used in studies on AUD. We then outline several future perspectives.

1. Incentive salience (IS) domain

The IS construct refers to the process by which repeated and excessive substance consumption leads to the progressive attribution of motivational significance to substance-related cues. These cues include not only the substance itself, but also contextual and interoceptive stimuli surrounding consumption, such as environmental settings, social context, emotional states, and bodily sensations (Koob & Volkow, 2016). In this framework, repeated exposure results in the transformation of previously neutral stimuli into salient and attractive motivational targets. The IS domain encompasses interrelated phenomena including reward, incentive salience and habit formation. It draws on the concepts of incentive motivation and conditioned reinforcement, whereby cues previously paired with substance effects gain the capacity to drive motivated behavior (Kwako et al., 2016). Through repeated substance use, incentive salience mechanisms play a central role in the emergence of craving, impaired reward learning and the transition from

goal-directed action to habitual and ultimately compulsive drug use (Kwako et al., 2016; Litten et al., 2015). The IS domain has been linked to the binge-intoxication stage of Koob's addiction cycle (Koob & Volkow, 2016; Kwako et al., 2016) that involves the basal ganglia circuitry and is associated with changes in dopamine and opioid peptides within the mesocortico-limbic system (Koob & Volkow, 2016; Litten et al., 2015).

In most ANA-specific studies, this domain is approached through self-reported scales or items assessing craving, obsessive thoughts related to alcohol, difficulty resisting consumption, and habitual drinking behaviors. Gunawan further expands this domain by incorporating alcohol insensitivity described as « *an individual's response to the effects of alcohol and amount of consumption when there is zero cost* » (Cofresí et al., 2025; Gunawan et al., 2024). Both Gunawan and Kwako also report the presence of negative affective components, which load on the two domains of IS and NE (Gunawan et al., 2024; Kwako et al., 2019). (Table 1)

2. Negative emotionality (NE) domain

The NE domain refers to negative affects, dysphoria, and hypohedonia, which are frequently exacerbated in individuals with chronic problematic substance use (Kwako et al., 2016). During chronic alcohol use, a process of stress sensitization develops and consumption is maintained not only for its rewarding properties but as a means of alleviating negative emotional states and withdrawal-related symptoms. Concurrently, reduced sensitivity to natural reinforcers and diminished motivational salience of non-substance-related stimuli emerge. This domain has been associated with the withdrawal and negative affect stage of the addiction cycle, involving, among other neural and neuroendocrine systems, the ventral striatum, the extended amygdala, and the

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hypothalamic-pituitary-adrenal axis (Koob & Moal, 1997; Koob & Volkow, 2016; Kwako et al., 2016; Litten et al., 2015).

In the ANA-specific literature, investigation of the NE domain primarily relies on questionnaires and items assessing trait or state depressive and anxiety symptoms, or more broadly negative affect, as well as aggressiveness, certain personality traits (neuroticism, low extraversion, low agreeableness), and alexithymia. (Table 1) Across studies, more than twenty different scales have been used, either in full or partially. Among these, the Beck Depression Inventory (BDI) and the State–Trait Anxiety Inventory (STAI) are the most frequently employed. Within this NE domain, Gunawan and colleagues also evaluate the Connor–Davidson Resilience Scale, whose score demonstrates a negative loading on the domain in their factor analysis.

3. Executive function (EF) domain

The EF domain proposed by Kwako and colleagues encompasses cognitive processes including "*attention, response inhibition, planning, working memory, behavioral flexibility, and valuation of future events*" (Kwako et al., 2016) as those functions are frequently impaired in addictive disorders. The dynamic interconnection and mutual reinforcement between the different stages and corresponding domains of addiction are particularly evident at this level (Koob & Volkow, 2016). Indeed, impaired executive control results in enhanced impulsivity and reduced capacity to regulate behavior when confronted with the incentive salience attributed to substance-related cues and with negative emotional states, further reinforcing maladaptive substance-seeking behaviors (Kwako et al., 2016). At this stage, two forms of craving develop, namely reward craving associated with cue-induced seeking behavior and relief craving reflecting negative reinforcement mechanisms (Litten et al., 2015). By interacting with incentive salience mechanisms, impaired executive function plays

a critical role in the transition from goal-directed actions to habit formation and compulsive behaviors. All this contributes to the persistence of addictive behaviors despite adverse consequences. This domain has been linked to the Preoccupation–Anticipation stage of the addiction cycle and to dysfunction within the prefrontal cortex (PFC) through multiple neurocircuitry pathways, including disrupted GABAergic activity and glutamatergic projections (Koob & Volkow, 2016).

Across the ANA studies, the EF domain is mainly assessed using questionnaires measuring impulsivity, particularly the Barratt Impulsiveness Scale and the UPPS-P Impulsive Behavior Scale. (Table 1) With the aim of focusing on alcohol-specific processes, items addressing control over alcohol consumption, effort required to resist craving and intrusive alcohol-related thoughts, and loss of control have been proposed (Boness et al., 2024; Votaw et al., 2023; Witkiewitz et al., 2023). Gunawan further expanded this domain by showing that questionnaires assessing metacognition and interoception load on this domain (Gunawan et al., 2024). EF is also investigated with behavioral paradigms, mainly focusing on working memory, attention, inhibition and flexibility. (Supplemental Table A)

4. Limitations and challenges of the ANA model

The ANA model provides a promising framework for addiction research and holds considerable clinical potential. However, substantial challenges remain. Two key limitations warrant priority attention: (1) the harmonization of domains assessment and (2) the use of integrated multimodal assessment combining self-reported, behavioral and neuroscientific measures for robust and reliable domain-specific evaluation.

An important first step would be to clarify and standardize the assessment of the three domains. More than 40 different questionnaires have been used to derive these domains, with studies relying most often on exploratory factor analysis (EFA) (Nieto et al., 2021) or confirmatory factor analysis (CFA) (Stein et al., 2021), and more rarely on principal component analysis (PCA) (Kirsch et al., 2024), as well as on individual items, subscale scores, or total scores. The lack of uniformity in questionnaire selection is partly understandable, as most ANA studies were based on retrospective datasets, offering limited control over the instruments originally administered. More concerning, however, is the inconsistent assignment of certain items between domains across studies, depending on the conceptual perspective adopted: whether the focus is on broad domain-level constructs or on more specific alcohol-related items that map more closely onto the stages of the addiction cycle as conceptualized by Koob. For example, Alcohol Dependence Scale (ADS) item 25 – *"After taking one or two drinks, can you usually stop?"* – was classified as IS by Stein et al. (2021) but as EF by Witkiewitz et al. (2023), while Obsessive Compulsive Drinking Scale (OCDS) item 13 – *"How strong is the drive to consume alcohol?"* – was assigned to IS by Kwako et al. (2019) and to EF by Witkiewitz et al. (2023). Some measures, such as the State-Trait Anxiety Inventory-Trait, load onto more than one domain, notably IS and NE (Gunawan et al., 2024; Kwako et al., 2019). The observed ambiguities in item/questionnaire attribution likely reflect the fact that the domains are statistically intercorrelated and biologically intertwined, given the extensive connectivity and overlap among the neural circuits involved. Gunawan and colleagues showed that three subfactors, alcohol motivation within IS, internalizing symptoms within NE, and impulsivity within EF, appear to drive much of these correlations (Gunawan et al., 2024). Standardizing domain assessment is therefore a challenge but an essential one, while keeping future clinical feasibility in mind. One option is to prioritize brief, already validated questionnaires (Parlier-Ahmad et al., 2023)

but with risk of the cross-loading; another is to develop new, targeted items specifically designed to capture these constructs more precisely (Votaw et al., 2023).

A second major objective is to use integrated assessments to improve the validity and reliability of domains-specific measurements. This will require multimodal studies combining self-report questionnaires, behavioral tasks, evoked potentials, neuroimaging, and biological samples. Although correlations between questionnaires and behavioral tasks are often weak (Gunawan et al., 2024), some studies have identified meaningful associations between alcohol-related self-report measures, behavioral indices, and neuroimaging data in specific regions (Al-Khalil et al., 2021). Voon et al. (2020) proposed investigating the three domains through neuroimaging by focusing on core processes including reward anticipation, negative emotionality, cue reactivity, impulsivity, compulsivity, and executive function (Voon et al., 2020). Functional connectivity studies have also provided evidence for brain correlates of the IS and NE domains, linking AUD severity to altered connectivity in reward, salience, and executive control circuits (Al-Khalil et al., 2021). Electrophysiological measures have likewise been proposed to investigate these domains (Jurado-Barba et al., 2020). Event-related potentials (ERPs) may serve as markers of vulnerability, severity, or clinical trajectory in alcohol use. For example, increased N1 and P3 amplitudes to alcohol-related cues suggest heightened incentive salience. In the EF domain, Go/No-Go paradigms could be used to assess inhibition deficits (Jurado-Barba et al., 2020). The P3b component from an Oddball task highlight the potential to distinguish different etiological mechanisms of alcohol use (Fein & Cardenas, 2017). ERPs may therefore become useful tools in precision medicine (Campanella et al., 2019). Research into molecular biomarkers is also expanding rapidly (Clark et al., 2025). Promising omics-based approaches include genomics, epigenomics, transcriptomics, proteomics, and metabolomics (Clark et al., 2025; Ho et al., 2024; Kwako et al., 2018; Volkow et

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al., 2015). These advances enable a more precise characterization of patient heterogeneity and improve our understanding of treatment response. Connections with the ANA domains can be considered (e.g., *IL17RB* genetic variants seem involved in response to acamprosate (Ho et al., 2024), a treatment that appears particularly relevant for patients with impairment in NE domain (Roos et al., 2017) ; epigenetic alterations in *CNR1* for IS and in *COMT* for EF (Kwako et al., 2018)). Although most biomarker studies remain at an early stage, they hold strong potential as complementary tools in multimodal approaches to precision medicine in addiction care (Clark et al., 2025).

Clarifying the associations between the different domains of addiction and specific brain regions, patterns of neural connectivity, ERPs, and molecular biomarkers, would substantially strengthen the neurobiological foundation of the ANA framework. At the same time, since ANA is intended to remain a clinically applicable tool, it is crucial to connect neurobiological findings with clinically accessible measures, including questionnaires and behavioral tasks. Standardizing ANA assessments in future prospective studies would be a major asset for enhancing the generalizability, comparability, and wider dissemination of results.

The use and systematic assessment of the three ANA domains could thus offer an opportunity to better characterize patient heterogeneity by relying on evidence-based constructs grounded in decades of neuroscience research on addiction. Such an approach should be actively supported within our field, where evidence-based interventions remain insufficiently implemented (Mekonen et al., 2021).

How recovery-inspired concepts can reinforce the ANA model

By focusing predominantly on a neurobehavioral framework linked to a neurobiological model, the ANA has been criticized since its inception for underemphasizing key non-brain dimensions. The importance of recovery-inspired dimensions as determinants of individual trajectories – strengths, social support, environment – but also as outcomes – quality of life – has been increasingly highlighted in the field and their integration into neuroscience-informed models of addiction advocated (Hagman et al., 2022; Volkow, 2020). Here, we propose such an approach. In this section, we first provide a brief overview of the recovery perspective and several of its key components. Secondly, we propose a fourth psycho-social domain to expand and strengthen the ANA model. Then, we insist on how additional recovery-inspired dimensions, related to strength-based components insufficiently reflected in the currently conceptualized ANA, can reinforce the different ANA domains. Finally, we emphasize the need for a holistic, global approach, made essential by the close interconnection between the various domains involved and we underscore the importance of higher-order evaluations, such as quality of life, a key indicator of this comprehensive approach and a cornerstone to the recovery process.

1. Recovery: a multi-facet concept

In the literature, different approaches of the term “recovery” are described: a *clinical recovery*, emerging from mental health services and focused on symptom reduction and improvement in functioning; and a *personal recovery*, developed by users and centred on personal change as well as life satisfaction (Provencher & Keyes, 2010; Slade et al., 2008). This *personal recovery perspective* places the individual at the centre of care, pragmatically aiming to improve future prospects and overall well-being through peer and group support, and a redefinition of identity, rather than to achieve a definitive cure per se through traditional medical care, thereby challenging classical notions of biological determinism (Heather et al., 2018; Pachoud, 2018). Such a

perspective is supported by the observation that 70% of people with alcohol-related problems are able to improve their condition without formal treatment, a phenomenon described in the literature as natural recovery (Tucker et al., 2020). However, this appears to be particularly common among individuals with lower disorder severity (Tuithof et al., 2014; Venegas et al., 2021). The "recovery" concept is now frequently used in an integrated manner to emphasize functioning, environmental context, individual strengths, and empowerment, reflecting a broader and more holistic understanding of mental health (Provencher & Keyes, 2010). Reflecting this evolution, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recently proposed its own operational definition of recovery from AUD – presenting recovery as a process and an outcome, insisting on symptoms reduction but also "*on the fulfilment of basic needs, enhancements in social support and spirituality, and improvements in physical and mental health, quality of life, and other dimensions of well-being*" (Hagman et al., 2022).

These dimensions – quality of life, socio-environmental dimensions and strengths – are central to clinical practice. If the ANA model is to achieve meaningful clinical impact, it must incorporate these elements. A more refined understanding of individual trajectories will depend on integrating neuro-cognitivo-biological vulnerabilities with patients' resilience and socio-environmental contexts (Kwako et al., 2016; Volkow, 2020; Witkiewitz et al., 2019). We therefore propose to complement the three ANA neurobehavioral domains. (Figure 1)

2. A psycho-social domain

Environmental context and social support are core components of the recovery perspective and represent essential dimensions of routine clinical care. The importance of those factors and social processes in AUD development (Goodwin & Sayette, 2022) and in relapse models is now well

established (Hunter-Reel et al., 2009; Karriker-Jaffe et al., 2020; Sliedrecht et al., 2019; Witkiewitz et al., 2019; Witkiewitz & Marlatt, 2009). Although Kwako and colleagues emphasized socio-environmental variables as important auxiliary dimensions for understanding AUD (Kwako et al., 2016), these factors remain barely integrated into ANA-based research. The inclusion of the social processes domain within the AARDoC framework was proposed from its inception (Litten et al., 2015) and continues to be regarded as essential – but lacking – for strengthening and refining the ANA approach (Garber & MacKillop, 2025). Insufficient attention to social processes has been identified as one factor limiting the translation of neuroscience research into clinical practice (Heilig et al., 2016). We therefore advocate that a domain focusing on psycho-social factors be included and studied within ANA research, in line with the recovery perspective but also with the RDoC Social Processes (SP) domain.

Social cognition impairments are frequent and multifaceted in AUD. They include deficits in facial affect decoding, prosody perception, theory of mind, empathy, and humour processing (Uekermann & Daum, 2008). Social difficulties are reflected in the literature on the ANA framework, but they have not been given a distinct place within the model. In the ANA study of Votaw and colleagues (Votaw et al., 2023) based on alcohol-specific items designed to map onto the addiction cycle, one of the statistical possibilities of the factor analysis was a four-factor structure with the fourth factor interpreted as a subdimension of the EF domain, specifically reflecting interpersonal conflict arising from cognitive impairment. In the three-factor solution, two items assessing interpersonal problems arising from deficits in cognitive control showed substantial cross-loadings, particularly on the NE factor. This pattern is coherent, given the emotional distress and negative affective consequences associated with interpersonal conflict (Votaw et al., 2023). The authors ultimately retained a three-factor model, aligning with the stages of the addiction cycle, and rejected these

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two items. In their narrative review, Jurado-Barba and colleagues theoretically associated alterations in emotional facial recognition with NE domain, as Kwako did (Jurado-Barba et al., 2020; Kwako et al., 2016). Gunawan and colleagues were the only to test the integration of the Inventory of Socially Supportive Behaviors in the NE domain, as suggested by Kwako's original paper, and the Experiences in Close Relationship Scale to test maladaptive attachment, as in the RDoC SP Domain (Gunawan et al., 2024). But those questionnaires didn't seem to load on the NE domain. We believe that, despite obvious connexions with the other domains, socio-environmental factors and processes deserve to be studied as an independent and distinct domain. (Supplemental Table B)

3. Strengths or resilience abilities as important factors

Understanding individual patient trajectories requires examining protective factors with the same rigor as risk factors for relapse. Under the umbrella term "strengths", we group determinants that have been consistently identified as central to relapse prevention (Sliedrecht et al., 2019; Witkiewitz & Marlatt, 2009), including positive coping strategies (Moos & Moos, 2006; Venkateswaran & Thirumalai, 2024), self-efficacy (Moniz-Lewis et al., 2022), and motivation to change (Senn et al., 2020). Those can be captured through validated questionnaires. (Supplemental Table B)

Here, we deliberately conceptualized patients' strengths as a distinct research area within a recovery-oriented perspective but these strengths-elements seem to be statistically related to the ANA domains. Indeed, Gunawan and colleagues have already initiate this perspective and were the first – and only – to explicitly add a "psychological strengths" subfactor – with resilience, extraversion and positive affects – and reported a negative loading between this one and NE

(Gunawan et al., 2024). Alcohol abstinence self-efficacy items appear to load on NE and IS (Witkiewitz et al., 2023). Alternatively, some strengths may operate as moderators of the impact of impaired ANA domains on relapse in the manner that motivation to change could be related to IS (Barnett et al., 2012; Folker et al., 2024) or EF (Luk & Thompson, 2024).

Clarifying the relationships between ANA domains and strength-related constructs is essential not only for elucidating relapse mechanisms but also for identifying actionable therapeutic targets. Highlighting, investigating, and cultivating patients' resources, rather than focusing exclusively on dysfunction, should be central to both research and clinical practice (Tauscher et al., 2021).

4. The importance of a global approach

The integration of a psycho-social domain and strength-related dimensions aims to provide a broader, more holistic view of patients. Considering patients across all domains, and clustering them accordingly, may support the identification of more homogeneous subgroups, improve the prediction of individual trajectories and ultimately help designing more tailored management strategies (Dacosta-Sánchez et al., 2021; Gunawan et al., 2024; Volkow, 2020). Far from diminishing the importance of detailed, domain-specific investigation, such an integrative framework helps place each domain into a coherent overall perspective.

Given the multiple interactions between the three ANA domains, the psycho-social domain and the strength dimensions, neglecting any of these components may hinder a full understanding of each patient's unique trajectory. For instance, exposure to an immediate environment in which alcohol cues are highly salient may disproportionately destabilize individuals with heightened cue reactivity from the IS domain. Interpersonal conflict may amplify negative affect in the NE domain, reduce perceived self-efficacy, and precipitate relapse. Conversely, positive social support can

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reinforce adaptive coping mechanisms and buffer high-risk situations, thereby preventing escalation into relapse (Hunter-Reel et al., 2009). Deficits in facial affect perception may lead individuals to infer hostile intentions where sadness is present, increasing the likelihood of interpersonal conflict (Kornreich et al., 2002) and negative affects, which in turn may contribute to relapse (Uekermann & Daum, 2008; Witkiewitz & Marlatt, 2009). Understanding all these complex and multidirectional interactions is also central to build appropriate care. In adolescents presenting with impaired IS, interventions designed to enhance motivation to change may be more clinically relevant than those primarily targeting EF (Folker et al., 2024). However, high motivation to change likely depends, at least in part, on preserved executive functions as decision-making capacities (Le Berre et al., 2013). Similarly, the emergence and maintenance of motivation to change require a belief in one's ability to succeed, that is, a relatively intact sense of self-efficacy. Several motivational interventions therefore act not only on readiness to change but also on strengthening self-efficacy (Barnett et al., 2012). Importantly, the development of self-efficacy is strongly influenced by positive social feedback and environmental reinforcement (Shany et al., 2022). These examples illustrate the dense network of interactions between strengths, neurobehavioral domains, and social factors.

All those elements will influence the quality of life. Quality of life offers a global and clinically meaningful perspective on patients' subjective appraisal of their condition. It can be seen as a higher-order, meta-domain factor, critical not only for monitoring outcomes, but also for capturing life satisfaction, that is central to recovery-oriented models and highly relevant to patients' everyday lived experience. (Supplemental Table B)

Taken together, these findings highlight the complex and bidirectional interactions between socio-environmental factors, patient strengths, and ANA domains. Future research integrating these

dimensions is needed to develop a comprehensive, holistic and dynamic framework capable of elucidating the relative contribution of each component, their feedback loop and their interplay within individual recovery trajectories. (Figure 1)

Therapeutic perspectives

Overall, the use of a framework such as the ANA, reinforced by neurobiological perspectives and expanded through recovery-oriented dimensions, provides a more integrative understanding of addiction while simultaneously paving the way for innovative and personalized treatment strategies. Such an approach has implications at several levels. Pharmacologically, it may help guide treatment selection according to the patient's specific profile (e.g., acamprosate in patients whose alcohol use is mainly driven by the relief of negative affect (Roos et al., 2017) and with specific IL17RB genetic variants (Ho et al., 2024) or naltrexone in those whose consumption is more strongly linked to reward-related effects (Mann et al., 2018)). Psychotherapeutically, interventions could be adapted to specific domain impairments (Boness et al., 2021; Boness & Witkiewitz, 2023). For instance, Behavioral Self-Control Training could be particularly adapted for patients with EF dysfunctions and Cognitive Behavioral Thearapy for AUD centred on emotion coping for patients with NE impairments (Boness et al., 2021). Luk and Thompson suggest adapting skills training component of Dialectical Behavioral Therapy, drawing on tailored coping strategies aligned with each patient's vulnerabilities on the ANA domain. For instance, the skill « STOP Skill » (Stop and resist, Take a step back, Observe, Proceed mindfully) can be used to address IS dysfunctions and to limit automatic behaviors triggered by alcohol-cue (Luk & Thompson, 2024). In a recovery-oriented perspective, they also explicitly target the various domains of quality of life (Luk & Thompson, 2024). In patients presenting with impairment in the socio-environmental domain, the use of couple- or family-based interventions, social skills remediation, or group

support may provide an opportunity to address dimensions that are still too often neglected in clinical care (Kaskutas, 2009; Le Berre, 2019; McCrady et al., 2016; Vaillant, 2005). A more refined understanding of the neural substrates underlying the different ANA domains, including regional brain activation, functional connectivity, and neurotransmitter systems, may, in the longer term, support the development of precision interventions based on non-invasive brain stimulation (Gibson et al., 2022).

Within such a framework, the ANA could help structure and align therapeutic strategies across levels of intervention, from psychotherapy and pharmacological treatment to neuromodulation approaches. The field is moving rapidly, and current translational efforts suggest that such integrative and neurobiologically informed approaches are increasingly relevant in addiction medicine (Boness & Witkiewitz, 2023; Rezapour et al., 2024; Williams et al., 2024).

Conclusion

The ANA framework represents a promising model for the translation of neurobiological research into clinical practice. To fully realize this potential, the current model would benefit from greater uniformity and further refinement in the self-reported assessment of its domains, alongside the development of multimodal strategies to capture each of them more comprehensively. In addition, the model should not remain confined to a strictly brain-centred perspective but rather integrate recovery-inspired dimensions that are essential to routine clinical practice and to the understanding of individual trajectories. This is the rationale behind our proposal to introduce a fourth psycho-social domain and to incorporate strength-based dimensions into the different ANA domains. Beyond their experimental relevance, these additions point toward a more integrated and holistic ANA model, one that is better aligned with the lived realities of clinicians and patients alike.

Ultimately, such a framework may help pave the way for genuinely personalized medicine in a population for whom it is urgently needed.

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Conflict of Interest

We declare no conflict of interest.

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Table 1. Questionnaires linked to the three domains in the ANA alcohol-centred studies

Incentive salience		Negative emotionality		Executive function	
Author generated	(Votaw et al., 2023) #3i	**Author generated**	(Votaw et al., 2023) #3i	**Author generated**	(Votaw et al., 2023) #5i
AASES	(Witkiewitz et al., 2023) #8, 9, 11, 15 (Boness et al., 2024) #8, 9, 11, 15	**AASES**	(Witkiewitz et al., 2023) #3, 6, 18 (Boness et al., 2024) #3, 6, 18	**ACQ-SF-R**	(Votaw et al., 2023) #1i inspired
ADS	(Kwako et al., 2019) #18 (Stein et al., 2021) #18, 25 (DeMartini et al., 2021) Total (Nieto et al., 2021) #Obsessive (Kirsch et al., 2024) #18, 25 (Gunawan et al., 2024) #18	**ACQ**	(Votaw et al., 2023) #1i inspired	**ADS**	(Witkiewitz et al., 2023) #25
AEQ	(Votaw et al., 2023) #1i inspired	**ACQ-SF-R**	(Votaw et al., 2023) #1i inspired	**AUDIDAS-5**	(Votaw et al., 2023) #1i inspired
AUDADIS5	(Votaw et al., 2023) #2i inspired	**AUI**	(Witkiewitz et al., 2023) #117	**AUI**	(Witkiewitz et al., 2023) #19, 124
AUDIT	(Nieto et al., 2021) #Consumption, Dependence, Problems	**ASI**	(Linn et al., 2023) Total	**BIS-11** [a]	(Kwako et al., 2019) #Attentional, Motor, Non planning (DeMartini et al., 2021) #Attentional*, Motor, Non planning (Gunawan et al., 2024) #Attentional, Motor, Non planning
DMQ	(DeMartini et al., 2021) #Coping motives*, Enhancement motives	**AUDIT**	(Kirsch et al., 2024) #7	**MCQ-30**	(Gunawan et al., 2024) #Cognitive self-consciousness, Lack of cognitive confidence, Need to control thoughts, Negative beliefs about uncontrollability and danger, Positive beliefs about worry
HPT	(Gunawan et al., 2024) # Demand intensity, Demand elasticity				
ICS	(Stein et al., 2021) #6, 13, 14, *23*	**BIS-11**	(DeMartini et al., 2021) #*Attentional**	**MC**	(Nieto et al., 2021) *(k)*
MRI	(Stein et al., 2021) #47	**BAI** [a]	(Votaw et al., 2020; Votaw et al., 2021) Total (Nieto et al., 2021) Total (Kirsch et al., 2024) Total	**MAIA**	(Gunawan et al., 2024) #Attention regulation, Body listening, Emotional awareness, Noticing, Self-regulation, Trusting
MADRS	(Kwako et al., 2019) Total (Gunawan et al., 2024) Total*	**BDI** [a]	(Votaw et al., 2020; Votaw et al., 2021) Total (Nieto et al., 2021) Total (Linn et al., 2023) Total (Kirsch et al., 2024) Total	**NEO PI-R**	(Kwako et al., 2019) #*Conscientiousness*
NAEQ	(DeMartini et al., 2021) #28	**BPAQ**	(Kwako et al., 2019) Total (Gunawan et al., 2024) #Anger, Hostility, Physical Aggression, Verbal Aggression	**OCDS**	(Witkiewitz et al., 2023) #6, 12, 13, 14 (Boness et al., 2024) #6, 12, 13, 14
OCDS [a]	(Kwako et al., 2019) #1, 11, 13 (Nieto et al., 2021) #Obsessive, Compulsive (Gunawan et al., 2024) #1, 11, 13	**BSI**	(Linn et al., 2023) #Anxiety, Depression, Hostility	**SSAGA**	(Votaw et al., 2023) #2i inspired
PACS	(Nieto et al., 2021) Total (Kirsch et al., 2024) Total (Gunawan et al., 2024) Total	**Brief WISDM**	(Votaw et al., 2023) #3i inspired	**DSM-IV SCI for ADHD**	(Kwako et al., 2019) Yes/No
SRE	(Gunawan et al., 2024) #First five times, Heaviest drinking	**CD-RISC**	(Gunawan et al., 2024) *Total*	**UPPS-P**	(Kwako et al., 2019) #Negative urgency, Premeditation, Perseverance, Positive urgency*

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SRHI	(DeMartini et al., 2021) Total (Votaw et al., 2023) #1i inspired
SSAGA	(Votaw et al., 2023) #1i inspired
SSS-A	(Folker et al., 2024) #6 items
STAI	(Kwako et al., 2019) #Trait* (Gunawan et al., 2024) #Trait*

DASS	(DeMartini et al., 2021) *#depression, anxiety*
DrInC	(Votaw et al., 2020; Votaw et al., 2021) #12, 16, 34
DMQ	(DeMartini et al., 2021) *#Coping motives**
MADRS	(Gunawan et al., 2024) Total*
NEO PI-R	(Kwako et al., 2019) *#Agreeableness, Extraversion,* Neuroticism (Gunawan et al., 2024) *#Agreeableness, Extraversion,* Neuroticism
PI	(DeMartini et al., 2021) *Total*
PANAS	(Linn et al., 2023) #Negative Affect (Gunawan et al., 2024) #Negative Affect, *Positive Affect* (Folker et al., 2024) #Negative Affect
STAI	(Kwako et al., 2019) #Trait* (Nieto et al., 2021) #Trait (Linn et al., 2023) #Trait (Gunawan et al., 2024) #Trait*
STAXI	(Votaw et al., 2020; Votaw et al., 2021) Total
TAS-20	(Gunawan et al., 2024) Total
UPPS-P	(Kwako et al., 2019) #Positive urgency*

	(DeMartini et al., 2021) #Negative urgency, Positive urgency (Gunawan et al., 2024) #Negative urgency, Premeditation, Perseverance, Positive urgency

Legend : [a] : questionnaire included in Kwako's original article (2016) ; **in red** : score, sub-score or item that loads on 2 domains (within the same study or in different studies) ; * : cross-loading on 2 domains in the same study ; **italics** : negative loading on the domain ; # : item number or sub-score ; **i** : item ; **AASES** : Alcohol Abstinence Self-Efficacy Scale ; **ACQ** : Alcohol Craving Questionnaire ; **ACQ-SF-R** : Alcohol Craving Questionnaire Short Form–Revised ; **ADHD**: Attention Deficit Hyperactivity Disorder ; **ADS** : Alcohol Dependence Scale ; **AEQ** : Alcohol Expectancy Questionnaire ; **AUDADIS-5** : Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 ; **AUDIT** : Alcohol Use Disorders Identification Test ; **ASI** : Anxiety Sensitivity Index ; **AUI** : Alcohol Use Inventory ; **BIS-11** : Barratt Impulsiveness Scale, version 11 ; **BAI** : Beck Anxiety Inventory ; **BDI** : Beck Depression Inventory ; **BPAQ** : Buss-Perry Aggression Questionnaire ; **BSI** : Brief Symptom Inventory ; **Brief WISDM** : Brief Wisconsin Inventory of Smoking Dependence Motives ; **CD-RISC** : Connor-Davidson Resilience Scale ; **DASS** : Depression Anxiety Stress Scales ; **DrInC** : Drinker Inventory of Consequences ; **DMQ** : Drinking Motives Questionnaire ; **HPT** : Hypothetical Purchase Task **; ICS** : Impaired Control Scale ; **MRI** : Marlatt Relapse Interview ; **MAIA** : Multidimensional Assessment of Interoceptive Awareness ; **MADRS** : Montgomery-Asberg Depression Rating Scale ; **MC** : Monetary Choice ; **MCQ30** : Metacognitions Questionnaire-30 ; **NAEQ** : Negative Alcohol Expectancy Questionnaire ; **NEO PI-R** : NEO Personality Inventory–Revised ; **OCDS** : Obsessive-Compulsive Drinking Scale ; **PACS** : Penn Alcohol Craving Scale ; **PANAS** : Positive and Negative Affect Schedule ; **PI** : Padua Inventory ; **SCI** : Structured Clinical Interview ; **SRE** : Self-Rating of the Effects of Alcohol Questionnaire ; **SRHI** : Self-Report Habit Index ; **SSAGA** : Semi-Structured Assessment for the Genetics of Alcoholism ; **SSS-A** : Sensation Seeking Scale

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(Adolescent-report) ; **STAI** : Spielberger State-Trait Anxiety Inventory ; **STAXI** : State-Trait Anger Expression Inventory ; **TAS-20** : Toronto Alexithymia Scale ; **UPPS-P** : UPPS-P Impulsive Behavior Scale

Figure Captions

Figure 1. An strengthened model

The current ANA framework, structured around its three core domains: Incentive Salience, Negative Emotionality and Executive Function, can be further enriched by incorporating recovery-oriented dimensions. The addition of a psychosocial domain, together with a more explicit integration of strength-based dimensions, allows for a broader yet more precise understanding of the patient's situation. Taken together, these elements are central to understanding patient outcomes, within which quality of life should be considered an essential component. Solid arrows indicate factors that may load negatively on a given domain; dashed arrows indicate factors that may moderate the effects of these domains on outcome; whereas the thick dotted arrow indicates that all the factors influence the outcomes.

Supplemental Material

Supplemental Table A. Behavioral tasks investigating ANA domain

Negative emotionality domain		Executive function domain	
Cyberball	(Gunawan et al., 2024) #Post-task emotional ratings	**CPT** [a]	(Gunawan et al., 2024) #D-prime
		DS	(Nieto et al., 2021) #Forward, Backwards (Gunawan et al., 2024) # Visual Backwards Two-error maximum length
		MTSO	(Gunawan et al., 2024) #Proportion correct
		MSIT	*(Folker et al., 2024) # SD of RT for correct responses in interference trials (reversed)*
		SBIT	*(Folker et al., 2024)# highest administered span minus total of failed items*
		SSRT [a]	(Gunawan et al., 2024) #Probability of responding in Stop trials #Covert stop signal reaction time
		TMT	(Gunawan et al., 2024) #Combined total time
		WCST [a]	*(Folker et al., 2024) #(-)Number of perseverative errors*

Legend : Underlined : item also present in Kwako's original article (2016) ; **italics** : negative loading on the domain ; **CPT** : Continuous Performance Test ; **DS** : Digit Span ; **MTSO** : Manikin Test of Spatial Orientation ; **MSIT** : Multi-Source Interference Task ; **SBIT** : Stanford Binet Intelligence Test ; **SSRT** : Stop Signal Reaction Task ; **TMT** : Trail Making Test ; **WCST** : Wisconsin Card Sorting Test.

Supplemental Table B. Propositions to investigate the recovery-inspired elements

Strengths		Psycho-social domain		
Dimension	**Questionnaire**	**Dimension**	**Questionnaire**	**Task**

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Coping strategies	CERQ (Garnefski & Kraaij, 2007; Garnefski et al., 2001)	Social support		SSQ6 (Sarason et al., 1987) ISSB (Barrera Jr et al., 1981)	
Self-efficacy	GSES (Schwarzer & Jerusalem, 1995) AASES (DiClemente et al., 1994)	Environmental context		WHOQoL-BREF #Environment (Group, 1998)	
Motivation to change	SOCRATES (Miller & Tonigan, 1996)	Social processes	Facial affect perception		Emotion recognition task (Montagne et al., 2007)
			Theory of mind		Visual perspective-taking task (Bukowski & Samson, 2016)
			Empathy	IRI (Davis, 1980)	
Meta-domain					
Dimension	**Questionnaire**				
Quality of life	WHOQoL-BREF (Group, 1998)				

Legend : AASE : Alcohol Abstinence Self-Efficacy Scale ; **CERQ** : Cognitive Emotional Regulation Questionnaire ; **GSES** : General Self-Efficacy Scale ; **IRI** : Interpersonal Reactivity Index ; **ISSB** : Inventory of Socially Supportive Behaviors ; **SOCRATES** : Stages of Change Readiness and Treatment Eagerness Scale, **SSQ6** : social support of Sarason questionnaire; **WHOQoL-BREF** : World Health Organization Quality of Life

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