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Attentional ERPs in consumers of smoked and insufflated cocaine associated with neuropsychological performance

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ABSTRACT

Background: Cocaine consumption is associated with reduced attentional event-related potentials (ERPs), namely P3a and P3b, indicating bottom-up and top-down deficits respectively. At cognitive level, these impairments are larger for faster routes of administration (e.g., smoked cocaine [SC]) than slower routes (e.g., insufflated cocaine [IC]). Here we assess these ERPs considering the route of cocaine administration. We hypothesized that SC dependent (SCD) would exhibit reduced amplitude of the P3a, while both SCD and IC dependent (ICD) would show reduced amplitude of the P3b.

Methods: We examined 25 SCD, 22 ICD matched by poly-consumption profiles, and 25 controls matched by demographic variables. We combined EEG data from the Global-Local task with behavioral data from attentional cognitive tasks.

Results: At the behavioral level, SCD exhibited attentional deficits in both bottom-up and top-down processes, while ICD only showed a tendency for top-down deficits. The amplitude of P3a and P3b was lower in Users groups. We observed subtle route-based differences, with larger differences in the P3a for SCD and in the P3b for ICD. Neurophysiological and behavioral data converged, with the P3a associated to bottom-up performance and P3b to top-down.

Conclusions: Different routes of administration lead to distinct attentional neurocognitive profiles. Specifically, SCD showed greater attentional impairment, mainly at bottom-up/P3a, while ICD showed a trend of top-down/P3b deficits. These findings emphasize the crucial role of considering the route of administration in both clinical and research settings and support the use of attentional ERPs as valid measures for assessing attentional deficits in substance Dependence.

1. Introduction

Smoked cocaine (SC) represents a major health risk among vulnerable populations in Latin America (Castaño, 2000; Castilla et al., 2020; Poder Judicial de la Ciudad de Buenos Aires, 2016). SC has a higher potential for Dependence than other slower routes of administration, such as insufflated cocaine (IC), as the former facilitates reinforcement and induces neuroplasticity changes in the reward system more easily (Allain et al., 2015; Oliveira et al., 2018; Samaha and Robinson, 2005). Our previous research has shown that, while overall cocaine Users

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exhibit executive-flexibility deficits measured by an extensive battery of cognitive tasks, attentional-executive impairments manifest solely in individuals with SC dependence (SCD), distinct from individuals with IC dependence (ICD) (de la Fuente et al., 2021). These findings align with clinical observations of heightened cognitive deficits in SC (Oliveira et al., 2018), alongside structural data indicating reduced gray matter density in the bilateral dorsal caudate in SCD compared to ICD (de la Fuente et al., 2021). However, the neurophysiological underpinnings of these deficits remain unexplored. To further define this subtle attentional-executive distinction, in this work we measured well-established attentional event-related potentials (ERPs), -which have been associated with substance use (Anderson et al., 2011; Biggins et al., 1997; Euser et al., 2012; Herning et al., 1994)-, on Users who differed only in the route of administration. By employing state-of-the-art attentional ERPs from oddball paradigm and a comprehensive attentional-executive neuropsychological assessment, we aimed to better understand the neural correlates of these cognitive deficits.

Three-oddball paradigms elicit the mismatch negativity (MMN), P3a and P3b components, reflecting pre-attentional, bottom-up, and top-down attentional processes, respectively (Conroy and Polich, 2007; Gooding et al., 2008; Heldmann et al., 2019; Hsieh et al., 2021). In passive tasks, infrequent stimuli evoke the MMN, unexpected or non-target stimuli evoke the P3a -with amplitude enhanced by the stimulus's salience-, and expected or target stimuli elicit the P3b, indicating attentional and executive processes (Carrasco, 2011; Desimone and Duncan, 1995; Friedman et al., 2001; Näätänen et al., 2007; Polich, 2007). In the context of neutral stimuli, studies have consistently shown bottom-up and top-down deficits signed by reduced P3a and P3b in Users of stimulants (Iwanami et al., 1998) and other drugs (Harper et al., 2021; Houston and Schlienz, 2018; Jurado-Barba et al., 2020; Maurage et al., 2007). When Users perform similarly to controls on cognitive tasks, they exhibit higher ERP amplitude, suggesting neural compensatory mechanisms (Campanella, 2021; Crego et al., 2012; Houston and Schlienz, 2018). Considering that factors such as drug-use level and drug type can impact the P3a and P3b (Polich and Criado, 2006), alongside the different cognitive profiles associated with SCD and ICD (de la Fuente et al., 2021), it is possible that these ERPs also vary according to the drug administration routes.

As attentional-executive deficits serve as a distinguishing factor between SCD and ICD, we aim to provide more clarity regarding the particular differences in the attentional process –encompassing both bottom-up and top-down aspects– that may arise due to variations in administration routes. For that reason, we conducted an analysis of attentional ERPs and hypothesized that SCD would exhibit reduced P3a/ bottom-up processes, while both SCD and ICD would show reduced P3b/ top-down processes. The impact of different cocaine administration routes on these attentional ERPs remains unclear, as most studies have not accounted for this relevant variable (Anderson et al., 2011; Campanella et al., 2019; Habelt et al., 2020; Wakim et al., 2021). Given the clinical relevance of these attentional ERPs in the context of substance use (Anderson et al., 2011; Biggins et al., 1997; Euser et al., 2012) and the distinct cognitive profiles associated with the route of administration, this study examines the differences in the P3a and P3b potential between SCD and ICD, and their relationship with neuropsychological performance in attentional tasks.

2. Materials and methods

2.1. Participants

The study included 72 subjects, 25 SCD, 22 ICD, and 25 controls (CTR) matched based on demographic variables (Table 1). Users fulfilled the DSM-IV criteria for and were classified into groups based on the drug that motivated their hospitalization and expert consensus of three addiction psychiatrists (Online Resources 1). Users were additionally matched by poly-consumption profile (Online Resources 1, Tables 1 and 2), ensuring they only differ in their preferred route of cocaine administration ($p < .05$). Controls were volunteers without a history of drug Dependence. Participants had no major psychiatric or neurological disorders or a high incidence of familial psychopathology (Online Resources 1, Table 3). Participants taking psychiatric medication were included only if the prescribed doses were below measurable at EEG (Macoveanu, 2014) (Online Resources 1, Table 4). All participants provided written informed consent. The study was approved by Favaloro University ethics committee (N∘ 609/16, record 554).

Table 1
Demography.

	CTR (N = 25)	SCD (N = 25)	ICD (N = 22)	Statistics
Age*	19.60 (2.62)	20.04 (2.28)	20.64 (2.96)	$F_{(2, 72)} = 0.91$, $p = .40$
Education*	9.47 (1.94)	8.76 (1.83)	9.45 (1.56)	$F_{(2, 72)} = 2.03$, $p = .14$
Biological sex (M: F)	22:3	23:2	21:1	$X^2 = 0.88$, $p = .64$
Handedness (R:L)	25:0	24:1	22:0	$X^2 = 1.91$, $p = .38$
ESOMAR (a:b:ca: cb:d:e)†	0:0:1:1:15:7	0:1:1:3:9:6	0:1:5:4:6:1	$X^2 = 15.46$, $p = .05$
NB (URB:SBN: Street)††	11:13:0	5: 11:1	13: 5:0	$X^2 = 8.45$, $p = .08$

† The European Society for Opinion and Marketing Research (ESOMAR) for socio-economical capacity categories are very-high (a), high (b), middle-high (ca), middle (cb), middle-low (d), and low (e).

†† unsatisfied basic needs (UBN), satisfied basic needs (SBN), or living in the street. CTR: Control; SCD: Smoked cocaine-dependent; ICD: cocaine hydrochloride-dependent.

* Values are expressed as mean (standard deviation).

2.2. Attentional cognitive tasks

Participants completed typical clinical attentional-executive tasks. To index bottom-up processes, we administered tasks focused on the basic aspects of the attentional domain, such as Trail Making Test (TMT) - A (Reitan and Wolfson, 1993), Trail 1 and Distractor List of the Rey-Auditory Verbal Learning Test (RAVLT) (Rey, 1941), Forward Digit span (Weschler, 1999), and Forward Corsi block-tapping test (Corsi, 1972). To index top-down processes, tasks tagging both attentional and executive function domains were included, such as Backwards Digit span (Weschler, 1999), Backwards Corsi block-tapping test (Corsi, 1972), Symbol-Digit Modality (Smith, 1973), TMT-B (Reitan and Wolfson, 1993), Letter and Number Sequencing Test (LNST) (Weschler, 1999), and Stroop test (Stroop, 1935). A detailed description of the tests and scoring can be found in the Online Resources 2.

2.3. Online attentional task during EEG

We used an adapted version (Gonzalez-Gadea et al., 2015) of the Global Local Task (Bekinschtein et al., 2009). This auditory oddball paradigm consists of sequences of 5 tones. The structure of the sequence determined the local level: local standard if 5 tones were equal, local deviant if the 5th tone was different –eliciting the MMN and P3a/bottom-up processes. This sequences repeated in blocks determining the global level: one sequence (either local standard or local deviant) presented 71.5 % of the time –stablishing a regularity and constituting a global standard trial-, and the opposite occurred 14.25 % -violating the regularity and constituting a global deviant trial. The remaining 14.25 % were interaural global standard, which was not analyzed in this study. Participants were instructed to pay attention and report the number of global deviations, which elicit the P3b. Detailed explanation in Online Resources 3.1.

2.4. High-density EEG data collection and preprocessing

Biosemi Active-two 128-channel system were used to record hd-EEG signals. Preprocessing was performed in Matlab (version 2014a, EEGLAB Toolbox), including resampling (256 Hz), band pass filtering (0.5–25 Hz), re-referencing (average), and interpolation (spherical method). EEG epochs were baseline corrected and noisy epochs were rejected using an automated procedure (Zich et al., 2015) and confirmed by visual inspection. We eliminated ocular artifacts using independent component analysis and generated grand-averages for each group by condition. For a detailed explanation refer to Online Resources 3.2.

2.5. Statistical analysis

2.5.1. Attentional cognitive tasks

To compare performance in individual cognitive tests and factor scores between groups we used non-parametric Kruskal-Wallis tests with Wilcoxon-Mann-Whitney tests for post hoc comparisons, corrected by False Discovery Rate (FDR) with a significance level given by *p*-FDR corrected <.05. Further analysis was restricted to cognitive test with significant differences between Users and CTR. We aimed to compress information from multiple cognitive tasks into two factors, reflecting bottom-up and top-down processes. We first performed a “theoretical expectation” analyzing how we would expect them to separate into these two factors. Next, we conducted a modularity analysis to confirm if two factors were the best fit within the modular structure (Online Resources 2.1). The theoretical expectation and modularity analysis were

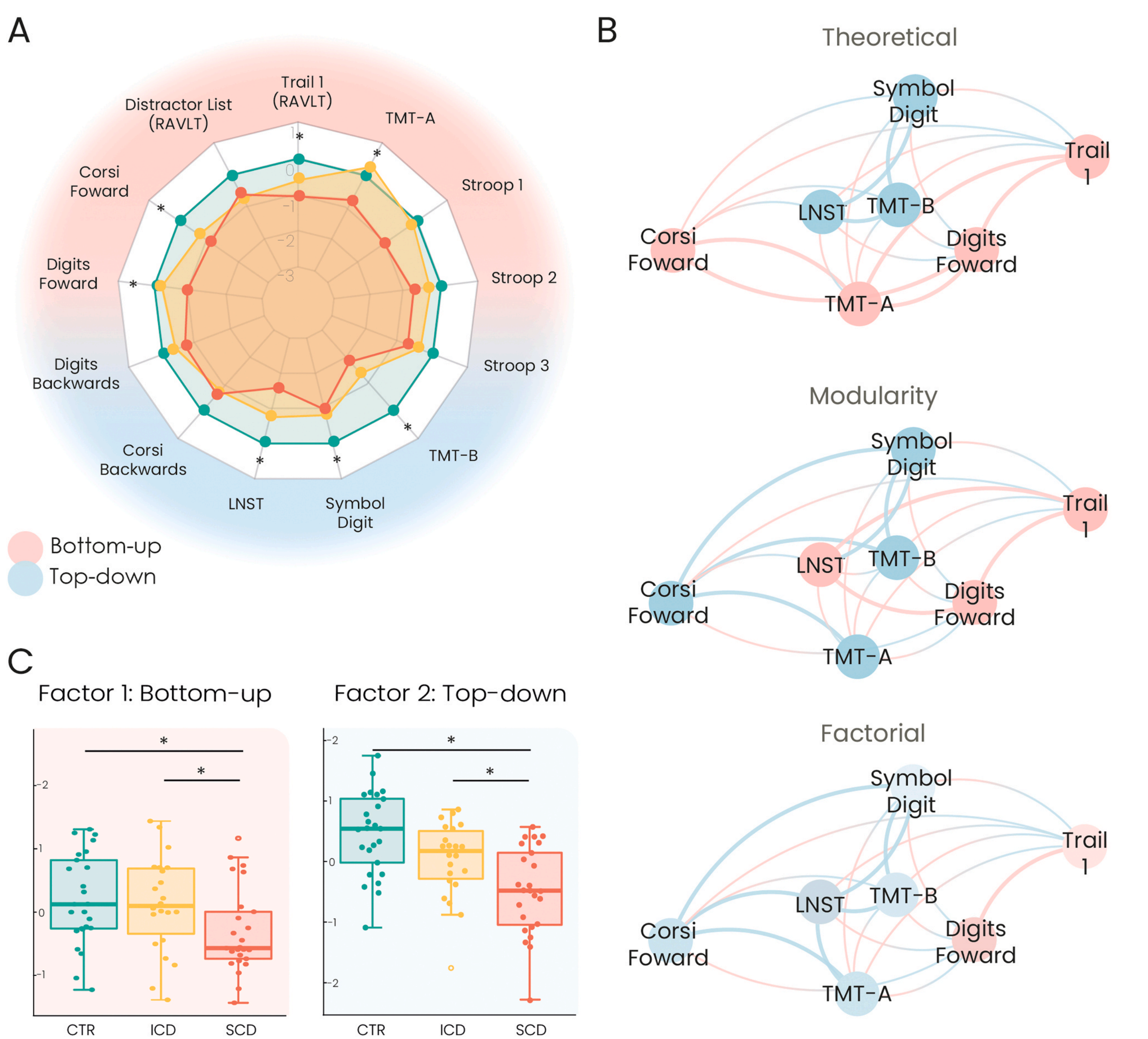

Fig. 1. Behavioral performance: A. Comparison of the performance of each group across neuropsychological tasks. The performance of the SCD (red) and ICD (yellow) groups is compared to the reference values for the CTR group (green). Statistical significance was determined using Kruskal-Wallis tests between groups. B. Graphs of task performance similarity, colored by domain (top), community structure (mid) and factorial analysis (bottom). In each of these graphs, the nodes represent a single task and the edges connecting them represent the correlation between the associated performances (i.e. the closer the nodes, the higher the correlation). C. Factor analysis of neuropsychological measures. The 2 factors (Bottom-up, Top-down) are named based on their factor load in individual tasks within both domains. * indicate significant differences (*p*-FDR corrected <0.05). RAVLT: Rey Auditory Verbal Learning Test; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; LNST: Letter- Number Sequencing Test; CTR: Control, N = 25; SCD: Smoked cocaine dependent, N = 25; ICD: insufflated cocaine dependent, N = 22.

convergent (see Results 3.1) so we performed a pre-defined two-factor exploratory factorial analysis based on Varimax rotation (Wassing et al., 2016) to obtain individual scores for two main factors using loading projection of original variables. Lastly, we constructed three graphs (Fig. 1B) maintaining the network structure but color-coded based on the theoretical expectations, modularity structure, and factorial analysis. Each cognitive task was a node connected by Spearman correlations (detailed explanation in Online Resources 2.1).

2.5.2. ERP analysis

ERP response between groups was compared using a point-by-point Monte Carlo permutation test with a minimum cluster extension of five consecutive points (de la Fuente et al., 2019; García-Cordero et al., 2016). MMN and P3a were analyzed from local deviant conditions (100–200 ms and 200–400 ms), and P3b in global deviant conditions (200–500 ms for ERP, 300–400 ms for maximum amplitude) (Bekinschtein et al., 2009; Gonzalez-Gadea et al., 2015). Expanding on our earlier findings, which identified a frontal correlate through structural and functional MRI with attentional-executive deficits (de la Fuente et al., 2021), we analyzed the ERP in a frontal region (Heldmann et al., 2019) of interest encompassing four electrodes (C25-C21-C12-C22 or Fz). Scalp topographies were calculated at the time point of maximal amplitude between each group of Users and CTR. The area over the curve (AOC) for P3a and P3b were used as representative measures of ERP amplitude (see Online Resources 4.1). Correlation analysis between ERP and cognitive data was performed by the Spearman correlation in R (version 4.1.2). Finally, for a comprehensive analysis involving all electrodes from the hd-EEG, we conducted a decoding analysis (King et al., 2014; King and Dehaene, 2014), using the publicly available MNE-Python script (https://mne.tools/stable/auto_tutorials/machine-learning/50_decoding.html). We employed a Logistic Regression model for binary classification. Decoder's performance was assessed using the AUC, with 50 % indicating random chance and a higher AUC reflecting improved predictive accuracy.

3. Results

3.1. Attentional cognitive tasks

SCD showed decreased performance with respect to CTR in Digits Forward, Corsi Forward, TMT-A, TMT-B, Symbol Digit, LSNT, and Trail 1 of RAVLT ($p < .05$, Fig. 1A). Also, SCD presented a reduced performance when compared to ICD in Digits Forwards and TMT-A ($p < .05$, Fig. 1A), while ICD did not differ significantly to CTR in any attentional test. See Online Resources Table 5 and de la Fuente et al., (2021) for further detail of the performance across multiple domains.

The theoretical expectations (Fig. 1B, top) and modularity analysis (Fig. 1B, mid) were consistent. The graph showed an optimal modularity of 0.006, with 2 modules accounting for 31 % and 18 % of all tasks. We subsequently conducted a factorial analysis (Table 2), which similarly reflected bottom-up and top-down processes.

Table 2
Factorial analysis.

NPS Variable	F1: Bottom-up	F2: Top-down
Digit forward	0.68	0.34
Trail 1 (RAVLT)	0.40	
TMT A*		0.54
TMT B*		0.43
Corsi forward		0.55
LNST	0.31	0.54
Symbol-Digit		0.31
Cumulative variance explained	31 %	18 %
Hypothesis test for 2 Factors: Chi-square (8) = 1.76, $p = 0.98$		

TMT A = Trail Making A; TMT B = Trail Making B; LNST = Letter-Number Sequencing Test; RAVLT = Rey- Auditory Verbal Learning Test.
* Variables inverted before factor analysis.

Finally, when comparing the performance of groups in the behavioral factors (Fig. 1C, further detail in Online Resources Table 6), we found that SCD performed poorer than both CTR and ICD in both factors (Bottom-up: $H_{(2, 72)} = 7.97$, $p = .01$, SCD vs. CTR $p = .02$, SCD vs. ICD $p = .03$; Top-down: $H_{(2, 72)} = 17.96$, $p < .001$, SCD vs. CTR $p < .001$, SCD vs. ICD $p = .03$). Although ICD did not differ from CTR, there is a tendency toward a decreased performance in the top-down factor than in the bottom-up (Bottom-up ICD vs. CTR $p = .77$; Top-down ICD vs. CTR $p = .06$).

3.2. Attentional ERP analysis

The Local-Global Task is illustrated in Fig. 2A. All groups elicit the attentional ERPs with a predominantly central topography (Online Resources, Fig. S1). There were no measurable differences the amount of ERP trials for each condition ($p > .05$, Online Resources, Table 7) or baseline conditions between the groups (Online Resources, Fig. S2). Both groups of Users exhibited a reduced amplitude of the P3a (Fig. 2B, left) and P3b (Fig. 2B, right) when compared to CTR (5000 permutations, $p < .05$), while there were no significant differences in the MMN ($p > .05$). For the P3a response, the cluster of significant differences between SCD and CTR (t = 301.6–399.2 ms) was 2.78 times longer (62.5 ms) than that of ICD and CTR (t = 313.3–348.4 ms), with no differences in latency ($H_{(2, 72)} = 1.07$, $p = .58$). Similarly, for the P3b response, the cluster of significant differences between ICD and CTR (t = 317.2–340.6 & 356.3 – 399.2 ms) was 1.7 times longer (27.2 ms) than that of SCD and CTR (t = 352.3–391.4 ms), with no differences in latency ($H_{(72, 2)} = 0.05$, $p = .97$). These differences were larger at frontal sites (Fig. 2B).

Notably, for the P3a, CTR and SCD classification achieved higher and extended in time accuracy than CTR and ICD. For the P3b, classification between CTR and ICD exhibited superior accuracy compared to CTR and SDC. These results indicate that the differences in the P3a were more prolonged in time for SCD, while in the P3b for ICD (Fig. 2B).

We found a significant association between the AOC of P3a and P3b ($r = .33$, $p = .005$) across samples that remain significant and stronger per groups only for CTRs ($r = .47$, $p = .01$; SCD: $r = .01$, $p = .9$; ICD: $r = .02$, $p = .37$), as observed in Fig. 2B (mid). Lastly, the ERPs were associated with the behavioral factors as expected (Fig. 2C): while the P3a was significantly associated with the bottom-up factor ($r = .27$, $p = .02$), the P3b was significantly associated with the top-down factor ($r = .23$, $p = .05$). There were no significant associations in the remaining two combinations (P3a with top-down factor, and P3b with bottom-up factor). Additional analysis per group is available in Online Resources 4.2.4.

4. Discussion

Although previous studies have identified deficits in bottom-up/P3a and top-down/P3b among cocaine Users, no study has explored the impact of the route of administration (Anderson et al., 2011; Bauer, 1997; Biggins et al., 1997; Gooding et al., 2008; Habelt et al., 2020; Houston and Schlienz, 2018; Wakim et al., 2021). Our study presents unprecedented evidence revealing differences in attentional ERPs based on the routes of administration. Our findings align with prior research indicating larger attentional deficits in SCD compared to CTR and ICD (de la Fuente et al., 2021; Oliveira et al., 2018), both at the neurophysiological and neuropsychological levels. Specifically, we observed pronounced impairments in the P3a component for SCD, along with greater attentional deficits in cognitive tasks. Moreover, we found more extensive differences in the P3b component for ICD. These results may contribute to the development of interventions targeted at specific attentional processes as well as a better understanding of the underlying mechanism of these deficits.

Regarding attentional neurocognitive performance, SCD displayed

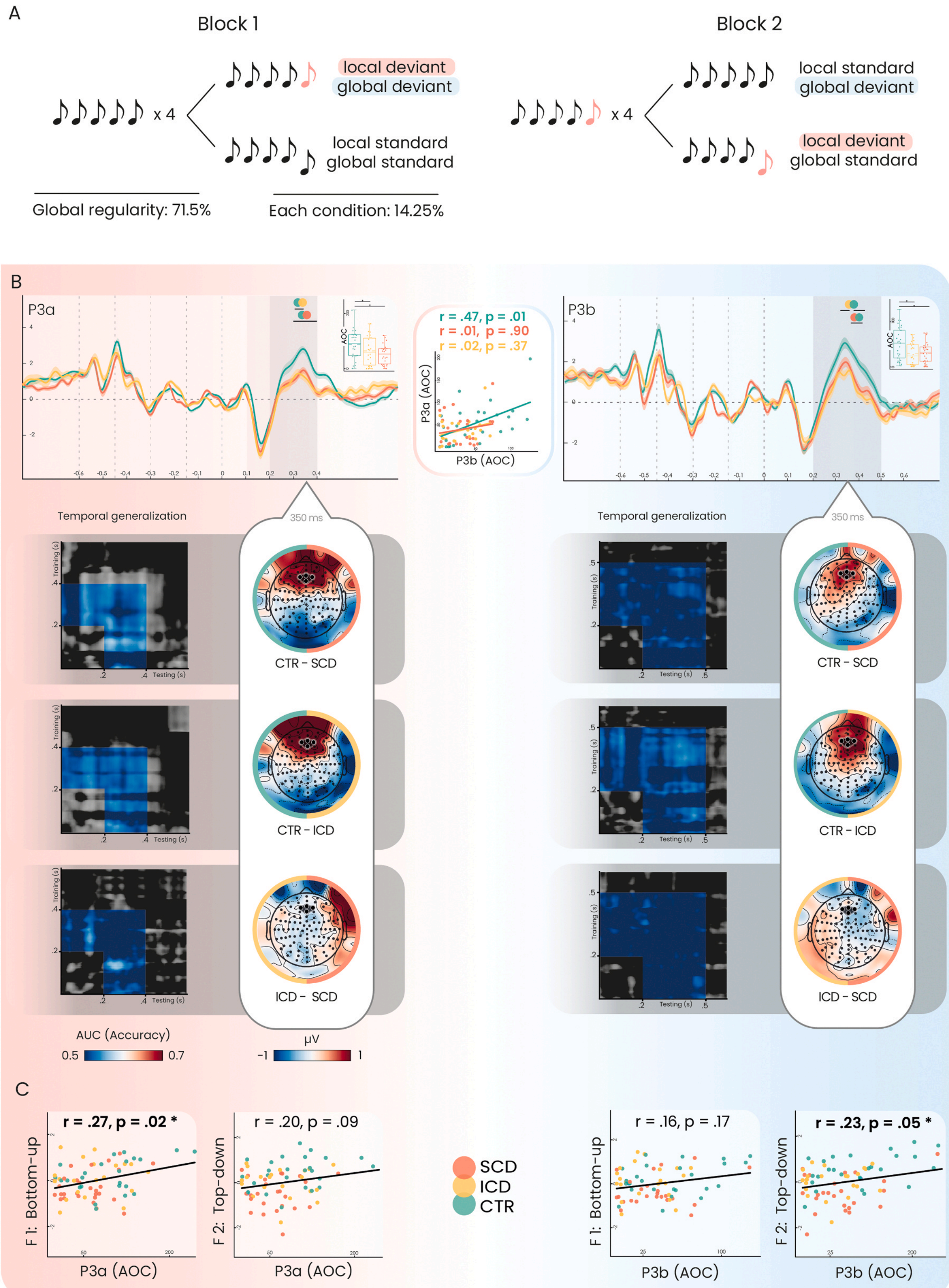

Fig. 2. ERP analysis. A. Global-Local Task. Auditory stimuli consisted of 5 tones type A (black) or B (pink) presented in 2 blocks. B. ERPs response, P3a and MMN (left) and P3b (right) in the ROI. All differences reported were calculated via a point-by-point Monte Carlo permutation analysis (5000 permutations, $p < .05$). Shadowed lines indicate SEM. The gray box indicates the area of analysis. Black lines indicate the cluster of significant differences and the circles and asterisk indicate the groups differing. The scatterplot in the middle shows the association between P3a and P3b AOC by group. Scalp topographies show the difference between each Users group and CTR at the ERP peak of amplitude time point. Matrices show the AUC of temporal decoding performance for each dyad comparison (left column for the P3a and right column for the P3b). C. Scatterplots show the correlation between both factors (Bottom-up and Top-down) and ERP measures (AOC of P3a and AOC of P3b). ld: local deviant; ls: local standard; gd: global deviant; gs: global standard; Int: interaural; AOC: area over the curve; CTR: Control, N = 25; SCD: Smoked cocaine dependent, N = 25; ICD: insufflated cocaine dependent, N = 22.

reduced values compared to CTR and ICD (see Table S5). The alignment between the theoretical expectations, modularity, and factorial analysis was notably high, particularly given that these attentional-executive tasks were not built under the bottom-up/top-down framework (for more detailed information, please refer to Online Resources 5.1). Specifically, Corsi Forward, TMT-A exhibited higher load on the top-down factor. This outcome is reasonable considering that cognitive tasks inherently involve varying degrees of executive functions, memory, and other cognitive domains (Goldstein et al., 2004), making it challenging to separate them into distinct factors. Particularly, Corsi Forward and TMT-A involve various complex cognitive functions, including visuospatial skills (Corsi, 1972; Reitan and Wolfson, 1993).

SCD exhibited reduced performance in both bottom-up and top-down processes compared to CTR and ICD. This finding aligns with previous studies that reported more pronounced attentional impairments for faster routes of administration (de la Fuente et al., 2021; Oliveira et al., 2018). While ICD did not significantly differ from CTR, there was a noticeable trend toward top-down impairment (p =.06), in agreement with research indicating impaired memory and executive function but not attentional deficits in ICD (de la Fuente et al., 2021; Oliveira et al., 2018). Nonetheless, our study shows comparable overall cognitive performance between ICD and CTR, contradicting the common association of cocaine consumption with decreased cognitive abilities (Romo-Avilés et al., 2015; Rosário et al., 2019; Vallejo-Reyes, 2019; Vergara-Moragues et al., 2017). This discrepancy may be attributed to methodological issues highlighted in a systematic review, indicating a lack of conclusive evidence supporting this relationship due to limitations in controlling demographic and polyconsumption variables (Frazer et al., 2018). Our study overcame these limitations and further examined the route of administration. Moreover, participants were adolescent (Grant and Dawson, 1998) who were currently in an abstinence state (Hirsiger et al., 2019; Vonmoos et al., 2014), which might account for the similar cognitive performance.

4.1. Electrophysiological markers of attention

At a pre-attentional level, we found no significant differences in MMN amplitude between the groups, indicating that early stages of auditory processing are preserved in cocaine Users regardless of the administration route. In line with previous studies associating decreased P3a/P3b amplitude with substance use (Anderson et al., 2011; Biggins et al., 1997; Euser et al., 2012), we found lower P3a and P3b responses in both groups of Users, with more pronounced differences in frontal areas for both ERPs. The fact that these differences were maximized at frontal sites is consistent with previous research showing the functional connectivity of inferior frontal areas and the caudate are correlated with attentional-executive deficits, particularly for SCD (de la Fuente et al., 2021). Our findings suggest that these alterations are common across different routes of administration, and they could either be associated with drug use (Hirsiger et al., 2019; Vonmoos et al., 2014) or show a vulnerability towards consumption (Harper et al., 2021; Tervo-Clemmens et al., 2018).

Regarding bottom-up attentional processing, SCD exhibited larger differences in the P3a and the decoding analysis showed SCD were distinguishable from CTR even after the P3a waveform, consistent with research at neurochemical, connectivity and cognitive levels. First, P3a relies on tonic dopamine levels (Heitland et al., 2013; Kähkönen et al., 2002; Rangel-Gomez et al., 2013), critical for attentional capture (Corbetta et al., 2008). SC has a strong impact on the reward system, leading to an increase in phasic dopamine in the short term and a decrease in tonic dopamine in the long term (Nieoullon, 2002; Samaha et al., 2004; Samaha and Robinson, 2005). Consequently, the greater attentional impairment in SCD is aligned with the pharmacokinetics of SC, which is characterized by rapid absorption, a strong effect and increased addictive behavior (Samaha et al., 2004; Samaha and Robinson, 2005). Second, the frontal regions involved in the P3a/bottom-up (Fjell et al., 2005; Friedman et al., 2001; Polich, 2007) exhibit disrupted connectivity in SCD (de la Fuente et al., 2021; Oliveira et al., 2018; Rosário et al., 2019). Altogether, these findings suggest that local processes related to attentional capture are more compromised in faster routes of administration. The fact that SCD-CTR differences extend for a longer period and extend toward the right, could be reflecting larger attentional deficits that extend in the cognitive continuum towards higher-order cognitive functions rather than perception (MMN). Even though ICD also presented lower P3a amplitude compared to CTR, these differences maintained for a shorter time window than those for SCD, pointing towards impaired cognitive processing in SCD encoded in waveforms (Botezatu et al., 2021; Brannon et al., 2008; Sabourin and Stowe, 2004; Togoli et al., 2022)-, and were not present at bottom-up cognitive level. Attentional deficits are a distinct signature of SCD (de la Fuente et al., 2021), and the lack of cognitive differences accompanying lower P3a amplitude in ICD may be due to the partial reversibility of drug-related cognitive deficits after abstinence (Hirsiger et al., 2019; Vonmoos et al., 2014) and the plasticity of adolescent brain (Grant and Dawson, 1998).

Regarding top-down processing, ICD exhibited more prolonged differences in the P3b, consistent with research at anatomical and cognitive levels. P3b is linked to memory processing in parietal regions (Polich, 2007) and ICD exhibit lower gray matter density over parietal areas compared to SCD and executive and memory impairments (de la Fuente et al., 2021). P3b differences were larger at the frontal site and extended towards central areas. While we focused on the differences in scalp topographies rather in the topography itself, it is true that the P3b traditionally exhibits a parietal topography. However, several studies have examined the P3b within a frontal ROI (Avancini et al., 2022; Li et al., 2015; Smith et al., 1990; Wood and McCarthy, 1985). Other studies have also documented the involvement of frontal lobes in P3b (Bachman and Bernat, 2018; Chennu et al., 2013; Friedman et al., 2001; Linden, 2005; Polich, 2007; Volpe et al., 2007) and variations in P3b topography (Avancini et al., 2022; Conroy and Polich, 2007; Fjell et al., 2005; Spyrou et al., 2006). Notably, a frontal shift in P3b topography is linked to changes in frontal cortical volumes (Fjell et al., 2005), which has been evidenced for this Users sample in a previous study (de la Fuente et al., 2021, 2019). Taken together, these findings suggest slower routes of administration primarily affect sustaining attention, which in turn may explain previous contradictory findings (Campanella et al., 2019; Houston and Schlienz, 2018). Along with the non-significant differences in top-down performance with CTR, these results point toward a reduced affectation for slower routes compared to faster routes, consistent with previous research (Allain et al., 2015; Castaño, 2000; de la Fuente et al., 2021; Meyer and Quenzer, 2019; Minogianis et al., 2013; Oliveira et al., 2018; Samaha and Robinson, 2005). Considering the convergence of cognition and ERP data, these distinct results for SC and IC highlight the significance of exploring the administration route. Furthermore, the shared physiology underlying attentional P3a and P3b warrants further examination, particularly in terms of their theoretical underpinnings for both top-down and bottom-up processes.

Finally, the association between P3a and P3b amplitude was observed in CTR but not in Users, regardless of the route of administration. Clinically, the absence of this association in Users is consistent with previous literature (Ma et al., 2014; Moeller et al., 2010; Orsini et al., 2018; Tomasi et al., 2007; Zhai et al., 2022) and their lower ERPs response and cognitive performance. This may be attributed to alterations in the prefrontal and parietal cortex among cocaine Users (Ma et al., 2014; Moeller et al., 2010; Orsini et al., 2018; Tomasi et al., 2007; Zhai et al., 2022), which play a crucial role in bottom-up and top-down processes (Buschman and Miller, 2007; Katsuki and Constantinidis, 2014; Li et al., 2013; Posner and Petersen, 1990; Yamaguchi et al., 2000). Theoretical implication of this finding are detailed in Online Resources 5.1.

Although our cross-sectional study cannot identify vulnerability or drug-derived impairment, these results might contribute to improving the treatment strategies. Considering addiction treatment's generally limited long-term efficacy (Agoos, 2017) and the high adolescent relapse rates (Cornelius et al., 2003), understanding the neurobiological factors in Users becomes crucial for innovative therapies (Feltenstein et al., 2021). Our findings linking fast cocaine administration to bottom-up deficits could inform tailored treatment strategies. For example, SCD may benefit from targeted neuropsychological rehabilitation for core attentional processes. Additionally, these cognitive symptoms must be considered in the broader clinical context (Ersche and Sahakian, 2007; Vergara-Moragues et al., 2017), potentially prompting adjustments in treatment session structures (further detailed in Online Resources 5.2). Moreover, considering prior research suggesting drug-related neurocognitive changes can partially reverse during abstinence (Hirsiger et al., 2019; Vonmoos et al., 2014), the observed ERP changes could serve to monitor treatment progress.

4.2. Limitations and further directions

The first limitation to this study is that the sample size was rather small, but we addressed this by controlling for demographic, clinical, and poly-consumption variables (Online Resources 1), which were not adequately controlled for in previous research. Consequently, the Users differed only in the route of administration (SC or IC), a relevant factor that is frequently overlooked in the literature (Frazer et al., 2018; Goldstein et al., 2004; Gooding et al., 2008; Lopes et al., 2017; Potvin et al., 2014; Vicario et al., 2020; Vonmoos et al., 2013; Wakim et al., 2021). Second, we had a larger proportion of male participants, although this reflects that the sample was drawn from a real-world clinical population as drug Dependence incidence is higher among males (Ángeles, 2013). Third, using ERPs has limitations due to their high variability, and lack of spatial resolution, and, while P3a and P3b are expected to index different processes (Conroy and Polich, 2007; Gooding et al., 2008; Hsieh et al., 2021), both of them refer to instances of attention and thus overlap temporally and spatially (Heldmann et al., 2019), making them not separable. The basic question regarding the convergence of bottom-up - P3a and Top-down - P3b exceeds our current scope, but even while is supported by our results it must be further analyzed. However, this distinction is supported by the convergence of behavioral and neuropsychological data.

Fourth, the cognitive tasks used were not specifically designed to measure bottom-up and top-down processes, although some have been previously used for this purpose (Araneda et al., 2015; Gevers et al., 2015; Schneider et al., 2014). Future studies could employ tasks designed for these processes (e.g., Posner, 1980) as well as explore in depth how the P3a and P3b separation can be maximized. Lastly, our study is cross-sectional, highlighting the need for future longitudinal studies to explore the relationship between neurocognitive deficits and cocaine intake.

5. Conclusions

Our results cast a new light on decreased attentional ERP response based on the route of cocaine administration, finding subtle yet significant differences. SCD showed greater attentional impairment, mainly at bottom-up/P3a processes, while ICD showed a trend towards top-down/P3b deficits. This indicates that faster routes of administration are associated with larger attentional capture deficits, while slower routes are linked to difficulties in sustaining attention. Longitudinal research studies suggest a bidirectional relationship between attention deficits and substance use (Harper et al., 2021; Hirsiger et al., 2019; Tervo-Clemmens et al., 2018; Vonmoos et al., 2014) and our findings suggest that the route of administration may play a key role in determining the severity of these deficits. These findings highlight the importance of considering the route of administration of stimulant drugs in both clinical and research settings. The route of cocaine administration is linked to distinct neurocognitive profiles, and our study yields translational results that align neurophysiological and neuropsychological levels. Furthermore, our findings strengthen the validity of utilizing attentional ERPs as reliable measures for assessing attentional deficits in the context of substance Dependence.

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CRediT authorship contribution statement

Rosario Figueras: Data curation. **Pilar Prado:** Data curation. **María Luz González-Gadea:** Writing – review & editing, Resources. **Lucia Lizaso:** Data curation. **Agustina Aragón-Daud:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Laura Alethia de la Fuente:** Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Teresa Torralva:** Writing – review & editing, Visualization, Supervision, Project administration, Conceptualization, Methodology. **Sofía Schurmann Vignaga:** Data curation. **Sofía Milagros Oberti De Luca:** Data curation. **Carla Pallavicini:** Investigation, Supervision, Writing – review & editing. **Marcelo Cetkovich:** Conceptualization, Investigation, Writing – review & editing. **Facundo Manes:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

M. Cetkovich declares he has received monetary compensation as a speaker from Gador, Lundbeck, Abbott, Pfizer, Baliarda, Roemmers, TEVA, Janssen, and Grunenthal in the last 3 years. The other authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2024.111288.

References

Agoos, J., 2017. Relapse and Recovery in Addictions. Yale University Press.
Allain, F., Minogianis, E.-A., Roberts, D.C.S., Samaha, A.-N., 2015. How fast and how often: the pharmacokinetics of drug use are decisive in addiction. Neurosci. Biobehav. Rev. 56, 166–179. https://doi.org/10.1016/j.neubiorev.2015.06.012.
Anderson, N.E., Baldridge, R.M., Stanford, M.S., 2011. P3a amplitude predicts successful treatment program completion in substance-dependent individuals. Subst. Use Misuse 46, 669–677. https://doi.org/10.3109/10826084.2010.528123.
Ángeles, V., 2013. Pasta Básica de Cocaína. Cuatro décadas de historia, actualidad y desafíos. Of. las Nac. Unidas Contra la Drog. y el Delito.
Araneda, R., De Volder, A.G., Deggouj, N., Philippot, P., Heeren, A., Lacroix, E., Decat, M., Rombaux, P., Renier, L., 2015. Altered top-down cognitive control and auditory processing in tinnitus: evidences from auditory and visual spatial stroop. Restor. Neurol. Neurosci. 33, 67–80. https://doi.org/10.3233/RNN-140433.
Avancini, C., Jennings, S., Chennu, S., Noreika, V., Le, A., Bekinschtein, T.A., Ring, H., 2022. Exploring electrophysiological markers of auditory predictive processes and

pathological ageing in adults with Down's syndrome. Eur. J. Neurosci. 56, 5615–5636. https://doi.org/10.1111/ejn.15762.
Bachman, M.D., Bernat, E.M., 2018. Independent contributions of theta and delta time-frequency activity to the visual oddball P3b. Int. J. Psychophysiol. 128, 70–80. https://doi.org/10.1016/j.ijpsycho.2018.03.010.
Bauer, L.O., 1997. Frontal P300 decrements, childhood conduct disorder, family history, and the prediction of relapse among abstinent cocaine abusers. Drug Alcohol Depend. 44, 1–10. https://doi.org/10.1016/S0376-8716(96)01311-7.
Bekinschtein, T.A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., Naccache, L., 2009. Neural signature of the conscious processing of auditory regularities. Proc. Natl. Acad. Sci. USA 106, 1672–1677. https://doi.org/10.1073/pnas.0809667106.
Biggins, C.A., MacKay, S., Clark, W., Fein, G., 1997. Event-related potential evidence for frontal cortex effects of chronic cocaine dependence. Biol. Psychiatry 42, 472–485. https://doi.org/10.1016/S0006-3223(96)00425-8.
Botezatu, M.R., Miller, C.A., Johnson, J., Misra, M., 2021. Event-related potentials reveal that bilinguals are more efficient in resolving conflict than monolinguals. Neuroreport 32, 721–726. https://doi.org/10.1097/WNR.0000000000001645.
Brannon, E.M., Libertus, M.E., Meck, W.H., Woldorff, M.G., 2008. Electrophysiological measures of time processing in infant and adult brains: Weber's law holds. J. Cogn. Neurosci. 20, 193–203. https://doi.org/10.1162/jocn.2008.20016.
Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315 (80), 1860–1864. https://doi.org/10.1126/science.1138071.
Campanella, S., 2021. Use of cognitive event-related potentials in the management of psychiatric disorders: towards an individual follow-up and multi-component clinical approach. World J. Psychiatry 11, 153–168. https://doi.org/10.5498/wjp.v11.i5.153.
Campanella, S., Schroder, E., Kajosch, H., Noel, X., Kornreich, C., 2019. Why cognitive event-related potentials (ERPs) should have a role in the management of alcohol disorders. Neurosci. Biobehav. Rev. 106, 234–244. https://doi.org/10.1016/j.neubiorev.2018.06.016.
Carrasco, M., 2011. Visual attention: the past 25 years. Vis. Res. 51, 1484–1525. https://doi.org/10.1016/J.VISRES.2011.04.012.
Castaño, G.A., 2000. Cocaínas fumables en Latinoamérica. Adicciones 12, 541–550.
Castilla, D.R., Matheu, F., Azzato, F., Milei, J., 2020. Productos intermedios de la cocaína: la pasta base o "paco". Rev. Asoc. Med. Argent. 133, 3–7.
Chennu, S., Finoia, P., Kamau, E., Monti, M.M., Allanson, J., Pickard, J.D., Bekinschtein, T.A., 2013. Dissociable endogenous and exogenous attention in disorders of consciousness. NeuroImage Clin. 3, 450–461. https://doi.org/10.1016/j.nicl.2013.10.008.
Conroy, M.A., Polich, J., 2007. Normative variation of P3a and P3b from a large sample: gender, topography, and response time. J. Psychophysiol. 21, 22–32. https://doi.org/10.1027/0269-8803.21.1.22.
Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324. https://doi.org/10.1016/j.neuron.2008.04.017.
Cornelius, J.R., Maisto, S.A., Pollock, N.K., Martin, C.S., Salloum, I.M., Lynch, K.G., Clark, D.B., 2003. Rapid relapse generally follows treatment for substance use disorders among adolescents. Addict. Behav. 28, 381–386. https://doi.org/10.1016/s0306-4603(01)00247-7.
Corsi, P.M., 1972. Human Memory and the Medial Temporal Region of the Brain. McGill Univ.
Crego, A., Cadaveira, F., Parada, M., Corral, M., Caamaño-Isorna, F., Rodríguez Holguín, S., 2012. Increased amplitude of P3 event-related potential in young binge drinkers. Alcohol 46, 415–425. https://doi.org/10.1016/j.alcohol.2011.10.002.
Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193–222. https://doi.org/10.1146/annurev.ne.18.030195.001205.
Ersche, K.D., Sahakian, B.J., 2007. The neuropsychology of amphetamine and opiate dependence: implications for treatment. Neuropsychol. Rev. 17, 317–336. https://doi.org/10.1007/s11065-007-9033-y.
Euser, A.S., Arends, L.R., Evans, B.E., Greaves-Lord, K., Huizink, A.C., Franken, I., 2012. The P300 event-related brain potential as a neurobiological endophenotype for substance use disorders: a meta-analytic investigation. Neurosci. Biobehav. Rev. 36, 572–603. https://doi.org/10.1016/j.neubiorev.2011.09.002.
Feltenstein, M.W., See, R.E., Fuchs, R.A., 2021. Neural substrates and circuits of drug addiction. Cold Spring Harb. Perspect. Med. 11 https://doi.org/10.1101/cshperspect.a039628.
Fjell, A.M., Walhovd, K.B., Reinvang, I., 2005. Age-dependent changes in distribution of P3a/P3b amplitude and thickness of the cerebral cortex. Neuroreport 16, 1451–1454. https://doi.org/10.1097/01.wnr.0000177011.44602.17.
Frazer, K.M., Richards, Q., Keith, D.R., 2018. The long-term effects of cocaine use on cognitive functioning: a systematic critical review. Behav. Brain Res. 348, 241–262. https://doi.org/10.1016/j.bbr.2018.04.005.
Friedman, D., Cycowicz, Y.M., Gaeta, H., 2001. The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neurosci. Biobehav. Rev. 25, 355–373. https://doi.org/10.1016/S0149-7634(01)00019-7.
de la Fuente, A., Sedeño, L., Vignaga, S.S., Ellmann, C., Sonzogni, S., Belluscio, L., García-Cordero, I., Castagnaro, E., Boano, M., Cetkovich, M., Torralva, T., Cánepa, E.T., Tagliazucchi, E., Garcia, A.M., Ibañez, A., 2019. Multimodal neurocognitive markers of interoceptive tuning in smoked cocaine. Neuropsychopharmacology 44, 1425–1434. https://doi.org/10.1038/s41386-019-0370-3.
de la Fuente, A., Vignaga, S.S., Prado, P., Figueras, R., Lizaso, L., Manes, F., Cetkovich, M., Tagliazucchi, E., Torralva, T., 2021. Early onset consumption of coca paste associated with executive-attention vulnerability markers linked to caudate-frontal structural and functional abnormalities. Drug Alcohol Depend. 227, 108926 https://doi.org/10.1016/j.drugalcdep.2021.108926.
García-Cordero, I., Sedeño, L., de la Fuente, L., Slachevsky, A., Forno, G., Klein, F., Lillo, P., Ferrari, J., Rodriguez, C., Bustin, J., Torralva, T., Baez, S., Yoris, A., Esteves, S., Melloni, M., Salamone, P., Huepe, D., Manes, F., García, A.M., Ibañez, A., 2016. Feeling, learning from and being aware of inner states: interoceptive dimensions in neurodegeneration and stroke. Philos. Trans. R. Soc. B Biol. Sci. 371 https://doi.org/10.1098/rstb.2016.0006.
Gevers, W., Deliens, G., Hoffmann, S., Notebaert, W., Peigneux, P., 2015. Sleep deprivation selectively disrupts top-down adaptation to cognitive conflict in the Stroop test. J. Sleep Res. 24, 666–672. https://doi.org/10.1111/jsr.12320.
Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.J., Fowler, J.S., Volkow, N.D., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447–1458. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2004.04.002.
Gonzalez-Gadea, M.L., Chennu, S., Bekinschtein, T.A., Rattazzi, A., Beraudi, A., Tripicchio, P., Moyano, B., Soffita, Y., Steinberg, L., Adolfi, F., Sigman, M., Marino, J., Manes, F., Ibanez, A., 2015. Predictive coding in autism spectrum disorder and attention deficit hyperactivity disorder. J. Neurophysiol. 114, 2625–2636. https://doi.org/10.1152/jn.00543.2015.
Gooding, D.C., Burroughs, S., Boutros, N.N., 2008. Attentional deficits in cocaine-dependent patients: converging behavioral and electrophysiological evidence. Psychiatry Res. 160, 145–154. https://doi.org/10.1016/j.psychres.2007.11.019.
Grant, B.F., Dawson, D.A., 1998. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the national longitudinal alcohol epidemiologic survey. J. Subst. Abus. 10, 163–173. https://doi.org/10.1016/S0899-3289(99)80131-X.
Habelt, B., Arvaneh, M., Bernhardt, N., Minev, I., 2020. Biomarkers and neuromodulation techniques in substance use disorders. Bioelectron. Med. 6 https://doi.org/10.1186/s42234-020-0040-0.
Harper, J., Malone, S.M., Iacono, W.G., 2021. Parietal P3 and midfrontal theta prospectively predict the development of adolescent alcohol use. Psychol. Med. 51, 416–425. https://doi.org/10.1017/S0033291719003258.
Heitland, I., Kenemans, J.L., Oosting, R.S., Baas, J.M.P., Böcker, K.B.E., 2013. Auditory event-related potentials (P3a, P3b) and genetic variants within the dopamine and serotonin system in healthy females. Behav. Brain Res. 249, 55–64. https://doi.org/10.1016/J.BBR.2013.04.013.
Heldmann, M., Teichmann, S., Al-Khaled, M., Brüggemann, N., Münte, T.F., 2019. Processing of local and global auditory deviants in Parkinson disease: electrophysiological evidence for enhanced attention capture. Cogn. Behav. Neurol. 32, 31–38. https://doi.org/10.1097/WNN.0000000000000185.
Herning, R.I., Glover, B.J., Guo, X., 1994. Effects of cocaine on p3b in cocaine abusers. Neuropsychobiology 30, 132–142. https://doi.org/10.1159/000119148.
Hirsiger, S., Hänggi, J., Germann, J., Vonmoos, M., Preller, K.H., Engeli, E.J.E., Kirschner, M., Reinhard, C., Hulka, L.M., Baumgartner, M.R., Chakravarty, M.M., Seifritz, E., Herdener, M., Quednow, B.B., 2019. Longitudinal changes in cocaine intake and cognition are linked to cortical thickness adaptations in cocaine users. NeuroImage Clin. 21, 101652 https://doi.org/10.1016/J.NICL.2019.101652.
Houston, R.J., Schlienz, N.J., 2018. Event-related potentials as biomarkers of behavior change mechanisms in substance use disorder treatment. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 30–40. https://doi.org/10.1016/j.bpsc.2017.09.006.
Hsieh, M.H., Chien, Y.L., Gau, S.S.F., 2021. Mismatch negativity and P3a in drug-naive adults with attention-deficit hyperactivity disorder. Psychol. Med. https://doi.org/10.1017/S0033291720005516.
Iwanami, A., Kuroki, N., Iritani, S., Isono, H., Okajima, Y., Kamijima, K., 1998. P3a of event-related potential in chronic methamphetamine dependence. J. Nerv. Ment. Dis. 186, 746–751. https://doi.org/10.1097/00005053-199812000-00002.
Jurado-Barba, R., Sion, A., Martínez-Maldonado, A., Domínguez-Centeno, I., Prieto-Montalvo, J., Navarrete, F., García-Gutierrez, M.S., Manzanares, J., Rubio, G., 2020. Neuropsychophysiological measures of alcohol dependence: can we use EEG in the clinical assessment? Front. Psychiatry 11, 1–17. https://doi.org/10.3389/fpsyt.2020.00676.
Kähkönen, S., Ahveninen, J., Pekkonen, E., Kaakkola, S., Huttunen, J., Ilmoniemi, R.J., Jääskeläinen, I.P., 2002. Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study. Clin. Neurophysiol. 113, 1894–1902. https://doi.org/10.1016/S1388-2457(02)00305-X.
Katsuki, F., Constantinidis, C., 2014. Bottom-up and top-down attention: different processes and overlapping neural systems. Neuroscientist 20, 509–521. https://doi.org/10.1177/1073858413514136.
King, J.R., Dehaene, S., 2014. Characterizing the dynamics of mental representations: the temporal generalization method. Trends Cogn. Sci. 18, 203–210. https://doi.org/10.1016/j.tics.2014.01.002.
King, J.-R., Gramfort, A., Schurger, A., Naccache, L., Dehaene, S., 2014. Two distinct dynamic modes subtend the detection of unexpected sounds. PLoS One 9, 1–8. https://doi.org/10.1371/journal.pone.0085791.
Li, L., Gratton, C., Fabiani, M., Knight, R.T., 2013. Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. Neurobiol. Aging 34, 477–488. https://doi.org/10.1016/j.neurobiolaging.2012.02.025.
Li, Y., Wang, W., Liu, T., Ren, L., Zhou, Y., Yu, C., Hu, Y., 2015. Source analysis of P3a and P3b components to investigate interaction of depression and anxiety in attentional systems. Sci. Rep. 5, 17138 https://doi.org/https://doi.org/10.1038/srep17138.
Linden, D.E., 2005. The P300: where in the brain is it produced and what does it tell us? Neuroscience 11, 563–576 https://doi.org/https://doi.org/10.1177/107385840528052.

Lopes, B.M., Gonçalves, P.D., Ometto, M., dos Santos, B., Cavallet, M., Chaim-Avancini, T.M., Serpa, M.H., Nicastri, S., Malbergier, A., Busatto, G.F., de Andrade, A.G., Cunha, P.J., 2017. Distinct cognitive performance and patterns of drug use among early and late onset cocaine users. Addict. Behav. 73, 41–47. https://doi.org/10.1016/j.addbeh.2017.04.013.

Ma, L., Steinberg, J.L., Hasan, K.M., Narayana, P.A., Kramer, L.A., Moeller, F.G., 2014. Stochastic dynamic causal modeling of working memory connections in cocaine dependence. Hum. Brain Mapp. 35, 760–778. https://doi.org/10.1002/hbm.22212.

Macoveanu, J., 2014. Serotonergic modulation of reward and punishment: evidence from pharmacological fMRI studies. Brain Res. 1556, 19–27. https://doi.org/10.1016/J.BRAINRES.2014.02.003.

Maurage, P., Philippot, P., Verbanck, P., Noel, X., Kornreich, C., Hanak, C., Campanella, S., 2007. Is the P300 deficit in alcoholism associated with early visual impairments (P100, N170)? An oddball paradigm. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 118, 633–644. https://doi.org/10.1016/j.clinph.2006.11.007.

Meyer, J.S., Quenzer, L.F., 2019. Psychomotor stimulants: cocaine, ampheatamine, and related drugs. Psychopharmacology. Drugs, the Brain, and Behavior. Oxford University Press, New York, United States of America, pp. 391–428.

Minogianis, E.A., Lévesque, D., Samaha, A.N., 2013. The speed of cocaine delivery determines the subsequent motivation to self-administer the drug. Neuropsychopharmacology 38, 2644–2656. https://doi.org/10.1038/npp.2013.173.

Moeller, F.G., Steinberg, J.L., Schmitz, J.M., Ma, L., Liu, S., Kjome, K.L., Rathnayaka, N., Kramer, L.A., Narayana, P.A., 2010. Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. Psychiatry Res. Neuroimaging. https://doi.org/10.1016/j.pscychresns.2009.11.003.

Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin. Neurophysiol. 118, 2544–2590. https://doi.org/10.1016/j.clinph.2007.04.026.

Nieoullon, A., 2002. Dopamine and the regulation of cognition and attention. Prog. Neurobiol. 67, 53–83. https://doi.org/10.1016/S0301-0082(02)00011-4.

Oliveira, H.P., Gonçalves, P.D., Ometto, M., Santos, B., Malbergier, A., Amaral, R., Nicastri, S., Andrade, A.G., Cunha, P.J., 2018. The route of administration exacerbates prefrontal functional impairments in crack-cocaine users. Addict. Behav. 32, 812–820. https://doi.org/10.1037/adb0000410.

Orsini, C.A., Colon-Perez, L.M., Heshmati, S.C., Setlow, B., Febo, M., 2018. Functional connectivity of chronic cocaine use reveals progressive neuroadaptations in neocortical, striatal, and limbic networks. eNeuro 5. https://doi.org/10.1523/ENEURO.0081-18.2018.

Poder Judicial de la Ciudad de Buenos Aires, 2016. Informe Del Equipo De Investigacion Sobre Consumo De Paco En Cinturon Sur De La Ciudad Autonoma De Buenos Aires. Diagnostico Y Propuesta Legislativa. Ciudad de Buenos Aires.

Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019.

Polich, J., Criado, J.R., 2006. Neuropsychology and neuropharmacology of P3a and P3b. Int. J. Psychophysiol. 60, 172–185. https://doi.org/10.1016/j.ijpsycho.2005.12.012.

Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25. https://doi.org/10.1080/00335558008248231.

Posner, M.I., Petersen, S.E., 1990. The attention system of the human brain. Annu. Rev. Neurosci. 13, 25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325.

Potvin, S., Stavro, K., Rizkallah, É., Pelletier, J., 2014. Cocaine and cognition: a systematic quantitative review. J. Addict. Med. 8, 368–376. https://doi.org/10.1097/ADM.0000000000000066.

Rangel-Gomez, M., Hickey, C., van Amelsvoort, T., Bet, P., Meeter, M., 2013. The detection of novelty relies on dopaminergic signaling: evidence from apomorphine's impact on the novelty N2. PLoS One 8. https://doi.org/10.1371/journal.pone.0066469.

Reitan, R., Wolfson, D., 1993. The Halstead Reitan Neuropsychology Battery: Theory and Clinical Interpretation. Neuropychology Press, Tucson.

Rey, A., 1941. L'examen psychologique dans les cas d'encephopathie traumatique (The psychological examination of cases of traumatic encephalopathy). Arch. Psychol. 28, 286–340.

Romo-Avilés, N., Camarotti, A.C., Tarragona, A., Touris, C., 2015. Doing gender in a toxic world. Women and freebase cocaine in the City of Buenos Aires (Argentina). Subst. Use Misuse 50, 557–565. https://doi.org/10.3109/10826084.2014.991404.

Rosário, B.D.A., De Nazaré, M.D.F.S., Estadella, D., Ribeiro, D.A., Viana, M.D.B., 2019. Behavioral and neurobiological alterations induced by chronic use of crack cocaine. Rev. Neurosci. https://doi.org/10.1515/revneuro-2018-0118.

Sabourin, L., Stowe, L., 2004. Memory effects in syntactic ERP tasks. Brain Cogn. 55, 392–395. https://doi.org/10.1016/j.bandc.2004.02.056.

Samaha, A.N., Mallet, N., Ferguson, S.M., Gonon, F., Robinson, T.E., 2004. The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. J. Neurosci. 24, 6362–6370. https://doi.org/10.1523/JNEUROSCI.1205-04.2004.

Samaha, A.N., Robinson, T.E., 2005. Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol. Sci. 26, 82–87. https://doi.org/10.1016/j.tips.2004.12.007.

Schneider, K.K., Schote, A.B., Meyer, J., Frings, C., 2014. Genes of the dopaminergic system selectively modulate top-down but not bottom-up attention. Cogn. Affect. Behav. Neurosci. 15, 104–116. https://doi.org/10.3758/s13415-014-0320-9.

Smith, A., 1973. Symbol Digit Modalities Test: Manual. Western Psychological Corporation, Los Angeles, Calif.

Smith, M.E., Halgren, E., Sokolik, M., Baudena, P., Musolino, A., Liegeois-Chauvel, C., Chauvel, P., 1990. The intracranial topography of the P3 event-related potential elicited during auditory oddball. Electroencephalogr. Clin. Neurophysiol. 76, 235–248. https://doi.org/10.1016/0013-4694(90)90018-f.

Spyrou, L., Jing, M., Sanei, S., Sumich, A., 2006. Separation and localisation of P300 sources and their subcomponents using constrained blind source separation. EURASIP J. Adv. Signal Process. 1–10. https://doi.org/10.1155/2007/82912.

Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18, 643–662. https://doi.org/10.1037/h0054651.

Tervo-Clemmens, B., Simmonds, D., Calabro, F.J., Montez, D.F., Lekht, J.A., Day, N.L., Richardson, G.A., Luna, B., 2018. Early cannabis use and neurocognitive risk: a prospective functional neuroimaging study. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 713–725. https://doi.org/10.1016/j.bpsc.2018.05.004.

Togoli, I., Fornaciai, M., Visibelli, E., Piazza, M., Bueti, D., 2022. Neural signature of magnitude integration. bioRvix 1–31.

Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., Volkow, N.D., 2007. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. Brain Res. 1171, 83–92. https://doi.org/10.1016/J.BRAINRES.2007.06.102.

Vallejo-Reyes, F., 2019. Assessment of the executive function in cocaine paste dependent patients using a neuropsychological battery. Psykhe 28, 1–17. https://doi.org/10.7764/psykhe.28.1.1111.

Vergara-Moragues, E., Verdejo-García, A., Lozano, O.M., Santiago-Ramajo, S., González-Saiz, F., Betanzos Espinosa, P., Pérez García, M., 2017. Association between executive function and outcome measure of treatment in therapeutic community among cocaine dependent individuals. J. Subst. Abus. Treat. 78, 48–55. https://doi.org/10.1016/j.jsat.2017.04.014.

Vicario, S., Pérez-Rivas, A., de Guevara-Miranda, D.L., Santín, L.J., Sampedro-Piquero, P., 2020. Cognitive reserve mediates the severity of certain neuropsychological deficits related to cocaine use disorder. Addict. Behav. 107, 106399 https://doi.org/10.1016/j.addbeh.2020.106399.

Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., Maj, M., 2007. The cortical generators of P3a and P3b: a LORETA study. Brain Res. Bull. 73, 220–230. https://doi.org/10.1016/j.brainresbull.2007.03.003.

Vonmoos, M., Hulka, L.M., Preller, K.H., Jenni, D., Baumgartner, M.R., Stohler, R., Bolla, K.I., Quednow, B.B., 2013. Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. Br. J. Psychiatry 203, 35–43. https://doi.org/10.1192/bjp.bp.112.118091.

Vonmoos, M., Hulka, L.M., Preller, K.H., Minder, F., Baumgartner, M.R., Quednow, B.B., 2014. Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. Neuropsychopharmacology 39, 2200–2210. https://doi.org/10.1038/npp.2014.71.

Wakim, K.M., Freedman, E.G., Molloy, C.J., Vieyto, N., Cao, Z., Foxe, J.J., 2021. Assessing combinatorial effects of HIV infection and former cocaine dependence on cognitive control processes: a high-density electrical mapping study of response inhibition. Neuropharmacology 195, 108636. https://doi.org/10.1016/j.neuropharm.2021.108636.

Wassing, R., Benjamins, J.S., Dekker, K., Moens, S., Spiegelhalder, K., Feige, B., Riemann, D., Van Der Sluis, S., Van Der Werf, Y.D., Talamini, L.M., Walker, M.P., Schalkwijk, F., Van Someren, E.J.W., 2016. Slow dissolving of emotional distress contributes to hyperarousal. Proc. Natl. Acad. Sci. USA 113, 2538–2543. https://doi.org/10.1073/pnas.1522520113.

Weschler, D., 1999. Weschler Abbreviated Scale of Intelligence. Psychologycal Corporation, San Antonio, TX.

Wood, C.C., McCarthy, G., 1985. A possible frontal lobe contribution to scalp P300. Neurosci. Abstr. 11, 879.

Yamaguchi, S., Yamagata, S., Kobayashi, S., 2000. Cerebral asymmetry of the "top-down" allocation of attention to global and local features. J. Neurosci. 20, 1–5. https://doi.org/10.1523/jneurosci.20-09-j0002.2000.

Zhai, T., Gu, H., Salmeron, B.J., Stein, E.A., Yang, Y., 2022. Disrupted dynamic interactions between large-scale brain networks in cocaine users are associated with dependence severity. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. https://doi.org/10.1016/J.BPSC.2022.08.010.

Zich, C., Debener, S., Kranczioch, C., Bleichner, M.G., Gutberlet, I., De Vos, M., 2015. Real-time EEG feedback during simultaneous EEG-fMRI identifies the cortical signature of motor imagery. Neuroimage 114, 438–447. https://doi.org/10.1016/j.neuroimage.2015.04.020.