A Cognitive-Pharmacokinetic Computational Model of the Effect of Toluene on Performance

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Abstract

We developed a cognitive-pharmacokinetic computational (CPC) model to understand how pharmacoactive substances, such as caffeine and toluene, modulate cognition. In this integrated model, dynamic physiological mechanisms are simulated to predict concentrations of the solvent toluene in the brain, which modulates specific cognitive systems in a dose-response fashion over multiple hours. We used our CPC model to reanalyze the results from prior research that documented an increase in reaction time following exposure to toluene in several laboratory tasks with no change in accuracy. Our analysis provides tentative evidence that toluene affects motor execution, rather than attention or declarative memory.

Keywords: ACT-R; Toluene; Pharmacokinetic; Computational Models

Introduction

In cognitive science, there has been a growing trend toward incorporating neurological, physiological, and bodily factors into theories of cognition to improve our understanding of cognition. van Rijn et al. (2016) argued that theories of cognition should span multiple levels of abstraction, such as the computational, algorithmic, and implementational levels proposed by Marr (1982). Integrative models have the advantage of explaining phenomena that are difficult to explain with models cast at a single level, constraining and informing cognitive models, demonstrating physiological/neural plausibility of cognitive models, and enabling prediction at multiple time scales (e.g., milliseconds and hours).

Integrative models take several forms. For instance, embodied cognition encompasses a diverse set of views with a common emphasis on the central role for perceptual-motor systems, bodily states, and the environment in cognition (Wilson, 2002). Many views of embodied cognition posit a reciprocal relationship between cognition and bodily states, or a tight coupling between perception and action, whereas some even consider the environment as part of the cognitive system (Wilson, 2002). Another integrative approach incorporates physiological moderators of cognition, such as circadian rhythm, to explain changes in cognition due to sleep deprivation (Gunzelmann et al., 2009).

The benefits of integrated models have been demonstrated in several recent studies. For example, Turner et al. (2016) demonstrated that incorporating neural models into a sequential sampling model of inter-temporal decision making improved fit and cross-validation compared to the component models. Integrated models have also been used to understand how cognitive moderators, such as stress and fatigue, alter task performance. For example, Gunzelmann et al. (2009, 2012) developed integrated models to understand the detrimental effects of sleep deprivation on cognition. In the integrated models, the physiological dynamics of circadian oscillation and sleep homeostasis modulated specific cognitive mechanisms. One important insight gained from these integrated models was that sleep deprivation affects procedural memory in simple reaction time (RT) tasks (Gunzelmann et al., 2009) and declarative memory in arithmetic tasks (Gunzelmann et al., 2012). Dancy et al. (2015) used a similar approach to understand how the physiology of a startle response affects cognition. Their integrated model revealed that the startle response increases epinephrine and the behavioral consequences could be explained in terms of fluctuations in the level of noise in declarative memory.

Building upon these integrative approaches, we present a general model that we call a cognitive-pharmacokinetic computational (CPC) model to understand how pharmacoactive substances (PSs) modulate cognition. PSs include toxins (e.g., toluene), pharmaceuticals, and other chemicals (e.g., caffeine) that affect cognition. Although there is a robust literature showing that PSs impact behavior, there is little computational work investigating which cognitive mechanisms are affected by PSs. Cognitive models lack a theory detailing how PSs are metabolized across time, whereas physiological models lack a theory that can link physiological changes to behavioral and cognitive consequences.

By integrating these approaches, we can disentangle the

contributions of multiple cognitive systems to overall task performance and identify which cognitive system is affected by PSs. To test our CPC model, we focus on a chemical called toluene, a colorless and odorless solvent commonly found in products, such as paint and adhesives, and is present in many work environments. Several studies have shown that acute and chronic toluene exposure leads to performance deficits in terms of RT or accuracy on a wide array of cognitive tasks (Rahill et al., 1996; Tang et al., 2011). What remains unclear is which cognitive system is affected by toluene exposure. For example, RT could increase as a result of a slowdown in attentional processing, motor execution, or memory retrieval. We use our CPC model to distinguish between these competing explanations.

Data and Tasks

We developed a CPC model of the toluene exposure experiment reported in Rahill et al. (1996). In that experiment, six subjects completed a battery of cognitive tasks, once without toluene exposure and again with toluene exposure. The experiment was conducted in a chamber where the atmospheric level of toluene was precisely controlled. A battery of seven cognitive tasks was administered three times throughout each 8-hour condition: once upon entering the chamber, again at 150 minutes immediately following 15 minutes of exercise and 15 minutes of biological exposure analysis, and one last time at 330 minutes. In the toluene condition, the air concentration of toluene was maintained at 100 ppm for the first 6 hours, after which point no further toluene was released into the chamber. Rahill et al. (1996) found that toluene increased mean RT for six of the seven tasks without impacting accuracy.

We developed CPC models for a subset of the tasks that offered the greatest chance of differentiating between competing accounts of performance decrements due to toluene exposure. The tasks were the procedural memory task, the recognition memory task, and the arithmetic task. Collectively, these tasks form a discriminative test bed for evaluating competing explanations because each task engages cognitive mechanisms in the computational model to varying degrees and thus produce a different pattern of predictions depending on which mechanism is modulated by toluene. Furthermore, a viable model must meet the challenge of producing the following pattern of effects with a single mechanism: an effect of toluene on RT in the procedural and recognition memory tasks, but not the arithmetic task.

Procedural Memory Task

On each trial of the procedural memory task, the number 1, 2, 3, or 4 was presented on the screen. Participants were instructed to respond according to the following stimulus-response mapping: press one button if the number was 1 or 2 and press another button if the number was 3 or 4. The stimulus disappeared after a maximum of 600 ms. [1]

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[1] We interpreted the disappearance of the stimulus as a response deadline in each task. In the discussion, we note that this assumption
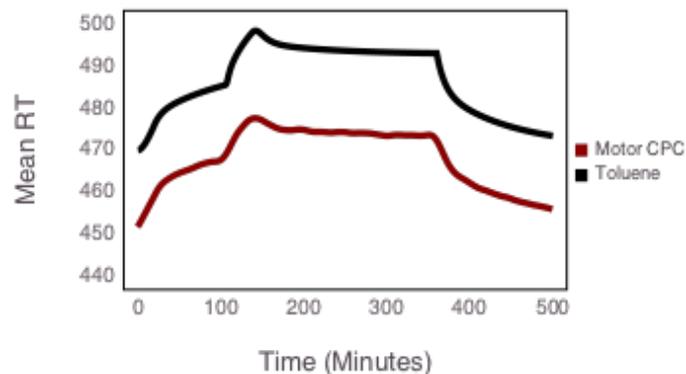

Figure 1: An illustration of the dose-response predictions of the motor CPC model for the procedural memory task. Toluene is rescaled in RT units for illustration.

Recognition Memory Task

During the learning phase, participants studied a set of six letters displayed simultaneously on the screen until they were confident the letters were committed to memory. Next, on each trial of the test phase, participants indicated whether or not a memory probe was in the studied list. The stimulus disappeared after a maximum of 850 ms.

Arithmetic Task

On each trial, a set of three single digit numbers were presented on the screen (e.g., 3 + 4 - 5) and participants indicated with the appropriate button whether the solution was less than or greater than 5. The stimulus disappeared after a maximum of 3,500 ms.

Cognitive-Pharmacokinetic Computational Model

The CPC model spans two levels of abstraction. At the physiological level, the physiologically-based pharmacokinetic pharmacodynamic (PBPK-PD) model describes the physiological dynamics that control the distribution and concentration of toluene. The output of the PBPK-PD model is the concentration level of toluene in the brain at a given point in time. At the cognitive level, the ACT-R cognitive architecture models the interplay of multiple cognitive systems during task performance. ACT-R and the PBPK models are integrated into a single model based on the assumption that toluene affects physiological and neural processes that support cognition, which in turn, affects performance. Figure 1 illustrates how mean RT for the motor CPC model tracks changes in toluene level in a dose-response fashion. We describe the sub-models and model integration in the following sections.

PBPK-PD Model

We used a PBPK-PD model to quantify the concentration of toluene in the brain throughout the exposure period (Tardif et al., 1997). The PBPK-PD model allows us to estimate the

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does not change core findings.

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amount of toluene in the brain and formulate dose-response predictions for task performance. A PBPK-PD model is an *in silico* representation of the movement of chemicals in the arterial blood, flowing to each major organ or lumped tissue compartment, including the brain.

PBPK-PD models calculate the time-course of PSs in the vascular and body tissues via ordinary differential equations to account for absorption, distribution, metabolism, and excretion processes. The following is an example differential equation of a metabolizing tissue:

$$\frac{dA_l}{dt} = (Q_l \times C_a) - \left(Q_l \times \frac{C_l}{P_l}\right) - \left(\frac{V_{Max} \times CV_l}{KM + CV_l}\right) \quad (1)$$

where subscripts l and a denote liver and arterial, respectively, A = amount of chemical (mg), Q = blood flow (L/hr), C = mg/L, KM = Michaelis-Menten constant (mg/L), P = tissue/blood partition coefficient, CV is venous concentration, and V_{max} = maximum rate of parent chemical change to metabolite (mg/hr).

There are three basic critical components to PBPK-PD models: 1) species-specific physiological parameters, 2) chemical-specific parameters, and 3) experiment-specific details for the studies to be simulated. As per convention, the physiological and chemical parameter values in our model were based on prior empirical measurement (Tardif et al., 1997). Species-specific physiological parameters are the organ weights and blood flow rates for the defined compartments (e.g., organs) in the PBPK-PD model and are derived from the closest like species when not available. Chemical-specific parameters that are unique for each chemical are the tissue solubility (partition coefficient), metabolism of the parent compound, and plasma and tissue binding characteristics. The specific experimental details pertain to the time of dosing and amount, route of dosing, and whether the subjects are physically active or quiescent. These details were obtained from Rahill et al. (1996).

Figure 1 shows the time-course of toluene concentration in the brain. Toluene increases rapidly from 135 to 150 minutes while the subject engages in exercise. Toluene concentration plateaus during rest then declines rapidly after the end of the 360-minute exposure period.

ACT-R

ACT-R is a cognitive architecture that specifies how modular cognitive systems interact to produce cognition and overt behavior (Anderson, 2007). Models developed within ACT-R posit a common set of processes and mechanisms, which are instantiated as a computer simulation. Independent modules operate in parallel and include declarative memory, vision, attention, and motor modules. Procedural memory coordinates the behavior of the architecture through a set of production rules. Production rules follow an "IF-THEN" structure that encodes the conditions under which specific actions are taken. ACT-R provides a structure within which potential explanations for the effect of toluene on cognition can

be formalized. For example, toluene might disrupt normal functioning of declarative memory, resulting in a slowdown in the retrieval of task-relevant information. We developed CPC models that formalize three explanations: toluene affects (1) declarative memory, (2) attention, or (3) motor execution. For brevity, we will refer to each of these explanations as the memory CPC, attention CPC, and motor CPC model, respectively.

The memory CPC model formalizes the hypothesis that toluene interferes with memory retrieval. In ACT-R, each fact stored in declarative memory—called a chunk— is associated with an activation value corresponding to the frequency and recency with which it has been used. Higher activation results in faster and more accurate retrieval. The declarative memory system in ACT-R offers several potential mechanisms for toluene modulation. Our criteria for selecting a mechanism were (1) it must be theoretically grounded and (2) it must produce a transient effect. We selected the parameter F_d because it produces a temporary decrease in activation and has been successful in accounting for the transient effect of fatigue on declarative memory (Gunzelmann et al., 2012). F_d scales base-level activation as follows:

$$b_i = F_d \cdot b_{LL} \quad (2)$$

where $F_d = [0,1]$, b_i is base-level activation for chunk i, b_{LL} represents activation associated with life-long learning (≈ 2.68; Gunzelmann et al., 2012). According to this explanation, toluene causes an acute decrease in activation, resulting in longer RTs and more errors. Decay, by contrast, has a destructive effect, which cannot be restored without additional practice.

The attention CPC model formalizes the hypothesis that the time required to attend to a stimulus is longer, resulting in a longer observed RT with no direct change in accuracy. Attentional processing time is controlled by increasing the attention latency parameter. The motor CPC model formalizes the hypothesis that toluene slows down the motor system, which increases RT without affecting accuracy. Motor execution is controlled by increasing the motor latency parameter.

Procedural Memory Model Declarative memory was populated with four chunks that encoded the response mapping. On each trial, the model attended to the number presented on the screen, retrieved a response mapping, and responded with the key specified in the retrieved chunk.

Recognition Memory Model Declarative memory was populated with chunks representing each letter in the alphabet. Once the list of six letters was presented, the model located a new letter starting on the left. After locating the letter, the model attended to the letter, and rehearsed it so as to strengthen its activation in memory. Throughout the course of the learning phase the model studied the list by repeating this cycle of productions. In Rahill et al. (1996), the learning phase was terminated by the subject when he or she was confident that the letters were memorized. However, no informa-

tion regarding the duration of the study phase was reported. We assumed participants studied the list for 10 seconds before proceeding to the test phase, which produced high accuracy found in similar studies (Levinson et al., 2005) with minimal time commitment. When a letter appeared during the test phase, the model attended to it, attempted to retrieve a chunk in memory that matched the letter and was in the study list, and executed a response. The model responded "yes" by key press if the retrieved letter matched the letter presented on the screen. If the letter did not match or no letter could be retrieved, the model responded "no" by key press.

Arithmetic Model   Declarative memory in the arithmetic model was populated with chunks representing arithmetic facts. Once the problem was presented (e.g., 3 + 5 - 2), the model processed each of the five components starting from left to right. First, the model located the leftmost stimulus (e.g., 3). Next, the model attended to the stimulus and then encoded the stimulus to keep track of the problem state. The model then repeated the procedure on the next stimulus (e.g., +). After encoding the first two numbers and operator, the model retrieved and then encoded the intermediate solution (e.g., 8). The model processed the remaining stimuli and retrieved the final solution (e.g., 8 - 2 = 6). Lastly, the model responded whether the solution was less than or greater than 5 via key press. If a math fact could not be retrieved, the model responded randomly.

Model Integration

The following equations provide a high-level representation of the model integration:

$$PBPK(\Lambda, t) = \tau \tag{3}$$

where Λ is a set of parameters, t is time since the beginning of the experiment, and τ is the predicted concentration of toluene in the brain. A high level representation of ACT-R is given by

$$ACTR_m(\Theta) = (RT, ACC) \tag{4}$$

where Θ is a set of parameters, $m \in \{$procedural, recognition memory, arithmetic$\}$ indexes the ACT-R models, and the tuple (RT, ACC) is the predicted mean reaction time and accuracy.

A linear link function allows specific ACT-R parameters to vary as a function of toluene level as follows:

$$\theta_p = \beta_{0_p} + \beta_{1_p} \tau \tag{5}$$

$p \in P = \{F_d, A, M\} \subset \Theta$ indexes the toluene-modulated ACT-R parameters, which correspond to fatigue declarative memory (F_d), attention latency (A), and motor latency (M). The intercept β_{0_p} is the value of parameter θ_p when the concentration level of toluene in the brain is zero. β_{1_p} is the slope which represents the degree to which θ_p varies as a function of τ. $\beta = \{\beta_{0_p}, \beta_{1_p}\}$ represents the set of link function parameters. Let $\hat{\Theta} = \Theta \setminus P$ be the subset of ACT-R parameters that are *not* determined from Equation 5 (e.g., latency factor).

Table 1: The slopes used in the link function of the CPC models. Slopes were varied over the ranges in brackets with 10 equal interval steps.

CPC Model	β_{1_A}	$\beta_{1_{F_d}}$	β_{1_M}
Attention	[0, .015]	0	0
Memory	0	[-.03, 0]	0
Motor	0	0	[0, .015]
Baseline	0	0	0

The CPC model integrates the ACT-R and PBPK-PD models through the linear link function and can be represented as:

$$CPC(\hat{\Theta}, \Lambda, \beta, t) = (RT, ACC) \tag{6}$$

We imposed the following parametric restrictions on the CPC models in the interest of parsimony. First, as shown in Table 1, we assumed that toluene affected only one cognitive system: either the attention, memory, or motor system. For example, in the attention CPC model, the slope β_{1_A} was allowed to vary while the other slopes were fixed to zero. As a basis for comparison, we also included a baseline CPC model in which no parameters were modulated by toluene. Second, we used the same parameterization of the link function across the three tasks. Specifically, when a slope was estimated, the estimated value applied across the three tasks. We also fixed the intercepts to $\beta_{0_A} = .085$ and $\beta_{0_M} = .05$, which are default values that have emerged as good fitting values across a wide range of studies. Because the intercept $\beta_{0_{F_d}}$ does not have a default value, we fixed this parameter to theoretically justified values of .72, 1, and .83 for the procedural, recognition memory, and arithmetic tasks, respectively, to reflect differences in prior exposure to task-specific stimuli. For example, subjects had more experience with the alphabet used in the recognition memory task than the response mapping used in the procedural memory task.

Third, when possible, we fixed other parameters to default values. For example, we fixed decay to .5. Mismatch penalty and activation noise do not have default values, and as such, were set to 2.8 and .15 for all models under consideration. Fourth, task-specific parameters were fixed across toluene conditions, blocks, and the four CPC models. Specifically, we set the retrieval threshold to .78 in the recognition memory task to control the speed of negative responses. Finally, the parameters of the PBPK-PD model were fixed to values acquired through prior empirical measurement.

Results

Human RTs (black) are displayed in Figures 2-4 for each task. Each panel represents an exposure condition, and points within each condition represent mean RT for a given block. Human RT increased in the toluene condition for the procedural and recognition memory tasks, but remained relatively constant in the arithmetic task. Although accuracy data were not reported in Rahill et al. (1996), no effect of toluene on ac-

Table 2: RMSE of best fitting models. PMT: procedural memory task, RMT: recognition memory task, AT: arithmetic task

| CPC Model | β_{1_p} | RMSE | | | |
		PMT	RMT	AT	Aggregate
Attention	.0015	10.13	28.04	92.30	56.00
Memory	-.003	10.87	30.33	89.24	54.78
Motor	.0045	9.59	23.40	90.17	54.07
Baseline	0	12.02	30.83	88.71	54.66
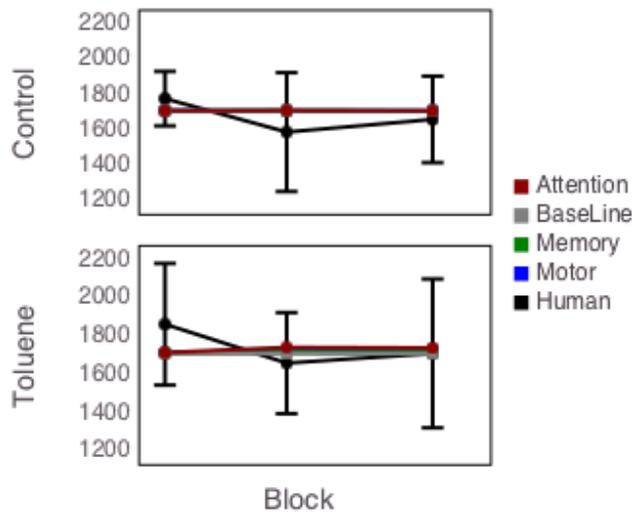
Figure 2: RT predictions for the CPC models plotted against the human mean RT for the Arithmetic Task. Bars are standard deviations.

curacy was detected. Based on other studies using the same or similar tasks, we assume that accuracy was $\geq 90\%$ (Levinson et al., 2005; Vincent et al., 2012).

We fit the four CPC models using the parameter ranges displayed in Table 1 and selected the best fitting models using a two-stage procedure. In the first stage, we selected the subset of results for which accuracy was $\geq 90\%$ in all blocks to ensure that the predictions were in line with previous studies. In the second stage, we selected the β_{1_p} with the lowest aggregate RMSE for each model. Table 2 summarizes aggregate RMSE, RMSE broken down by task, and the best fitting β_{1_p} for each model. The predictions of the best fitting CPC models are compared to the human data in Figures 2-4.

Aggregate RMSE was the lowest for the motor CPC model, suggesting that toluene slows down motor processing. Although the improvement in aggregate RMSE relative to the baseline model may appear small, it hides modest but important improvements in the procedural and recognition memory tasks. Importantly, the motor CPC model was able to capture the qualitative pattern of effects found in the human data: an effect of toluene in the procedural and recognition memory tasks with no effect in the arithmetic task.
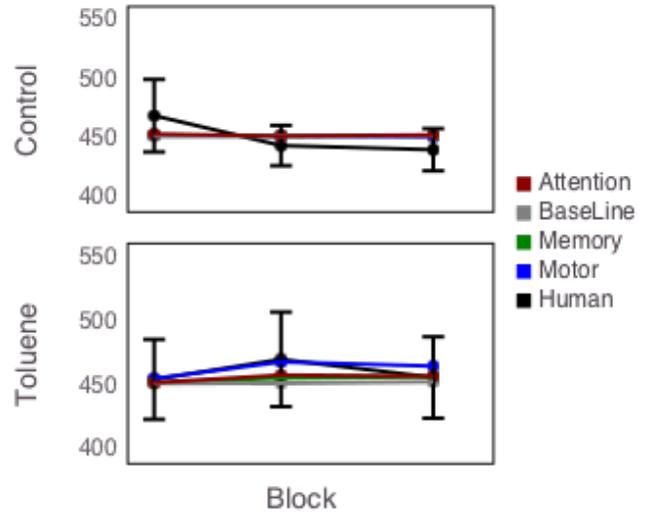

Figure 3: RT predictions for the CPC models plotted against the human mean RT for the Procedural Memory Task. Bars are standard deviations.
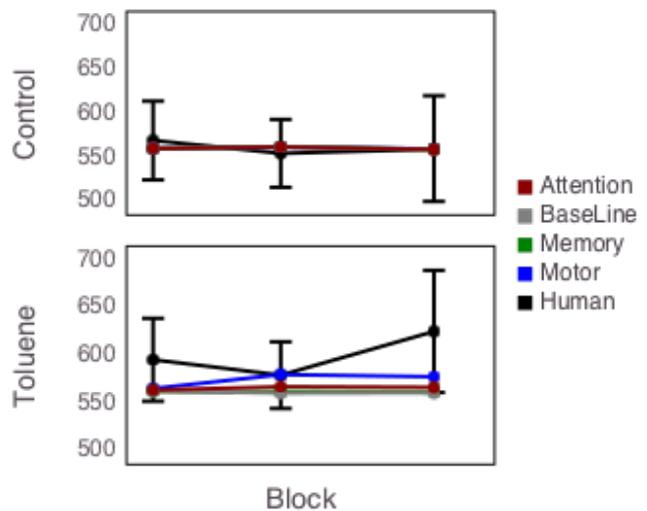

Figure 4: RT predictions for the CPC models plotted against the human mean RT for the Recognition Memory Task. Bars are standard deviations.

It is also informative to discuss patterns found in some poorly fitting CPC models. For example, when β_{1_A} increased for the attention CPC model, the RT predictions improved to a similar degree as the motor CPC model in the procedural and recognition memory tasks. In the arithmetic task, however, the attention CPC model greatly over-estimated RT due to the large contribution of attention to the overall RT. This finding provides further evidence against the attention CPC model.

Discussion

We developed and tested a set of CPC models to understand which cognitive systems are affected by toluene and lead to

the performance decrements reported in the literature. The CPC model integrated the physiological dynamics of toluene concentration into the ACT-R cognitive architecture to produce dose-response predictions over a prolonged period of toluene exposure. The CPC models formally instantiated deficits in memory, attentional, and motor processing as competing explanations for detrimental effects of toluene exposure. Our model comparison provided tentative evidence that performance decrements are driven by a slowdown in motor execution. Furthermore, we also found evidence against attention as a mechanism: when attention was modulated by toluene to the same extent as the motor system, it greatly overestimated RTs in the arithmetic task. Importantly, the motor CPC model produced the pattern of toluene effects in the human data: an effect of toluene in the procedural and recognition memory tasks, and no effect in the arithmetic task.

Our CPC model adds to the growing literature showing that integrated models can yield more accurate predictions and deeper insights compared to non-integrative approaches. The CPC model has several benefits. First, it enabled us to account for data at two different time-scales: on the order of milliseconds as well as hours. Second, the CPC model was powerful yet highly constrained. With the CPC model, we were able to account for the effects of toluene exposure in three tasks using a single mechanism. Moreover, other parameters were either set to default values or otherwise highly constrained. Third, the CPC model is quite general, allowing it to be applied to any PS of interest.

Limitations

Our findings should be interpreted in light of several limitations. First, research on PSs often has small sample sizes and small exposure manipulations due to restrictions imposed by institutional review boards to limit risk. As a result, discriminating among competing explanations is challenging and our conclusions regarding the motor CPC model remain tentative. Second, we also could not apply the model at the individual level or examine nuanced predictions (e.g., false alarms vs. misses) because only summary data were available. Third, our PBPK-PD model could not examine the possibility of region-specific effects of toluene in the brain. A model with this level of detail would provide tighter integration and more focused hypotheses about the affected mechanisms. Finally, we made assumptions about several unreported or ambiguous methodological details, such as the number of trials, the duration of the study phase in the recognition task, and the use of response deadlines. Nonetheless, when these assumptions were changed, the motor CPC still emerged with the strongest level of support.

Acknowledgments

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