

See discussions, stats, and author profiles for this publication at: http://www.researchgate.net/publication/258526409

Latent Toxoplasma gondii infection leads to improved action control

ARTICLE in BRAIN BEHAVIOR AND IMMUNITY · NOVEMBER 2013

Impact Factor: 6.13 · DOI: 10.1016/j.bbi.2013.11.004 · Source: PubMed



Brain, Behavior, and Immunity 37 (2014) 103-108

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Latent Toxoplasma gondii infection leads to improved action control

Ann-Kathrin Stock^{a,*}, Evelyn Heintschel von Heinegg^b, Hedda-Luise Köhling^b, Christian Beste^a

^a Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, University of Dresden, Schubertstrasse 42, D-01307 Dresden, Germany ^b Institute for Medical Microbiology, University Hospital Essen, Robert-Koch-Haus, Virchowstraße 179, D-45147 Essen, Germany

ARTICLE INFO

Article history: Received 9 September 2013 Received in revised form 5 November 2013 Accepted 5 November 2013 Available online 12 November 2013

Keywords: Toxoplama gondii Latent toxoplasmosis Parasite Human Manipulation hypothesis Dopamine Executive functions Action cascading EEG Stop-change paradigm

1. Introduction

Toxoplasma gondii (*T. gondii*) is one of the world's most successful parasites, having an estimated world-wide prevalence of 30–70% among human populations (Boothroyd and Grigg, 2002; Flegr, 2013; Webster, 2007).

T. gondii relies on several routes of transmission and infests a wide variety of warm-blooded hosts but it depends on finding its way into the digestive system of felidae (members of the family of cats) in order to reproduce sexually (Tenter et al., 2000). A "convenient" way to reach this goal is a latently infected secondary host (e.g. a rodent) falling prey to a cat. Therefore, *T. gondii* is believed to alter the behavior of its secondary host in order to increase the risk of predation. In this context, infected rodents have repeatedly been shown to display less neophobia, more exploratory behavior and to lose their natural fear towards cats (Berdoy et al., 2000; Vyas et al., 2007; Webster, 2007). This manipulation hypothesis is widely accepted (Moore, 1984; Webster, 2001) but the underlying biochemical mechanisms have only recently been discovered. When the parasite first enters a human host, it triggers the acute stage of

ABSTRACT

The parasite *Toxoplasma gondii* has been found to manipulate the behavior of its secondary hosts to increase its own dissemination which is commonly believed to be to the detriment of the host (manipulation hypothesis). The manipulation correlates with an up-regulation of dopaminergic neurotransmission. In humans, different pathologies have been associated with *T. gondii* infections but most latently infected humans do not seem to display overt impairments. Since a dopamine plus does not necessarily bear exclusively negative consequences in humans, we investigated potential positive consequences of latent toxoplasmosis (and the presumed boosting of dopaminergic neurotransmission) on human cognition and behavior. For this purpose, we focused on action cascading which has been shown to be modulated by dopamine. Based on behavioral and neurophysiological (EEG) data obtained by means of a stop-change paradigm, we were able to demonstrate that healthy young humans can actually benefit from latent *T. gondii* infection as regards their performance in this task (as indicated by faster response times and a smaller P3 component). The data shows that a latent infection which is assumed to affect the dopaminergic system can lead to paradoxical improvements of cognitive control processes in humans. © 2013 Elsevier Inc. All rights reserved.

infection during which it forms rapidly dividing tachyzoites that infect a number of different tissues (Gaskell et al., 2009; Robert-Gangneux and Dardé, 2012; Webster et al., 2013). Under the pressure of the host's innate immune response, the tachyzoites usually transform into the more slowly dividing bradyzoites, resulting in the latent stage of infection (Gaskell et al., 2009; Henriquez et al., 2009; Robert-Gangneux and Dardé, 2012; Webster et al., 2013). In immunocompetent individuals, a postnatal infection usually has a clinically asymptomatic progress and results in a lifelong immunity. Yet, the immune system cannot effectively eliminate the bradyzoites (see Henriquez et al., 2009; Robert-Gangneux and Dardé, 2012 for review) which encyst within muscle and brain tissue of the host organism where they may remain for as long as a lifetime (Henriquez et al., 2009; Kamerkar and Davis, 2012; Robert-Gangneux and Dardé, 2012; Tenter et al., 2000).

Previously, cytokines released by the host's immune system (e.g. interleukin 2) were assumed to mediate changes in host behavior (Alonso et al., 1993; Henriquez et al., 2009; Petitto et al., 1997). However, it was recently discovered that a different mechanism most likely accounts for the majority of behavioral changes associated with *T. gondii* infection: Both tachyzoites and bradyzoites have been shown to continuously produce tyrosine hydroxylase, the limiting factor of dopamine synthesis (Gaskell et al., 2009). It has been shown that in catecholaminergic neurons, this extra tyrosine hydroxylase ultimately results in an up-regulation of dopaminergic neurotransmission as characterized by increased dopamine





CrossMark

^{*} Corresponding author. Tel.: +49 (0)351 458 4259.

E-mail addresses: ann-kathrin.stock@uniklinikum-dresden.de (A.-K. Stock), Evelyn.heintschelvh@uk-essen.de (E. Heintschel von Heinegg), Hedda-Luise. Koehling@uk-essen.de (H.-L. Köhling), christian.beste@uniklinikum-dresden.de (C. Beste).

^{0889-1591/\$ -} see front matter @ 2013 Elsevier Inc. All rights reserved. http://dx.doi.org/10.1016/j.bbi.2013.11.004

As a consequence, all catecholaminergic neurons containing bradyzoite cysts produce and release more dopamine, irrespective of their location in the brain (McConkey et al., 2013). In addition to this, both behavioral changes and tachyzoite differentiation have been demonstrated to be prevented by dopamine antagonists such as haloperidol or GBR 12909 (Jones-Brando et al., 2003; Skallová et al., 2006; Webster et al., 2006).

Based on all of these findings, it is commonly assumed that the parasite's manipulation is to the adverse of the host (for review see Flegr, 2013; Webster, 2007). However, this does not necessarily need to hold true for humans. Even though different pathologies including schizophrenia, suicide and workplace accidents have been associated with latent T. gondii infections (Flegr, 2013; Treuer et al., 2007), most latently infected humans do not seem to display overt impairments or drastic changes in cognition and behavior (e.g. Kamerkar and Davis, 2012). Yet, T. gondii lacks the ability to distinguish between the many different host organisms it invades, so that all infested host organisms should experience an up-regulation of dopamine and display associated behavioral changes (irrespective of how "useful" this is for the parasite's distribution; Webster et al., 2013). This hypothesis has not been tested in all potential host organisms but Webster et al. (2013) noted that "altering host behaviour in 'inappropriate' hosts is plausibly an unavoidable consequence of parasite-altered behaviour" since "there would not be selective pressure for this specificity".

Based on the finding that an up-regulation of the dopaminergic system can increase cognitive flexibility (Cools et al., 2001; Schulz et al., 2012; van Holstein et al., 2011), we investigated whether latent *T. gondii* might also be advantageous to its human carriers.

For this purpose, a stop-change paradigm similar to that of Verbruggen et al. (2008) was employed. The task measures action cascading (stopping a response in favor of a different reaction) which can be considered as an aspect of cognitive flexibility. Dopamine has repeatedly been demonstrated to modulate executive processes including the inhibition of a (planned) response (Barnes et al., 2011; Chambers et al., 2009; Eagle and Baunez, 2010; Humphries et al., 2006; Ravizza et al., 2012; Robbins and Arnsten, 2009; Willemssen et al., 2009) as well as response selection/switching processes (Aarts et al., 2010; Avila et al., 2012; Cools et al., 2001; Garcia-Garcia et al., 2010; Humphries et al., 2006; Redgrave et al., 1999).

2. Materials and methods

2.1. Ethics statement

All participants gave written consent and were treated in accordance with the declaration of Helsinki. The study was approved by the ethics committee of the medical faculty of the University of Bochum.

2.2. Sample

The sample consists of 36 healthy right-handed volunteers (26 male, 10 female). Half of them (13 male, 5 female) had been diagnosed with a latent *T. gondii* infection. Due to a double-blind design, neither the participants nor the experimenters knew about the infection status at the time the experiment was conducted. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971); the mean overall EHI score was 0.89 (SD = 0.16). The mean age was 24.56 years (SD = 2.62). Further information on the characteristics of the sample is provided in Table 1. None of the participants presented with a history of psychiatric or neurological disease as reported in a customized questionnaire designed by experienced neuropsychologists. Each participant received a reimbursement of $10 \in$.

2.3. Assessment of T. gondii antibodies

The participants were classified as either Toxoplasma-positive or -negative based on the concentration of specific IgM and IgG anti-Toxoplasma antibodies in their sera. IgG and IgM antibodies were detected in the sera of the candidates using an Enzyme-linked Immunosorbent Assay (ETI-TOXOK-G-PLUS and ETI-TOXOK-M-reverse-PLUS; DiaSorin, Saluggia, Italy) running on a ETI-MAX 3000 (DiaSorin, Saluggia, Italy), a fully automated microtiter plate analyzer. Inactivated *T. gondii* (RH strain) from sonicated and extracted trophozoites serve as test antigen.

2.4. T. gondii-IgG

According to the instructions of the manufacturer, samples with absorbance values greater than that of the cut-off calibrator at 15 IU/mL should be considered reactive for specific IgG-antibodies to *T. gondii*. Samples with absorbance values less than or equal to 15 IU/mL should be considered nonreactive for IgG. Borderline concentrations of IgG ranging within $\pm 10\%$ of the cut-off value were retested. The diagnostic specificity of the IgG-test is 99.3% with a confidence level of 98.8–99.9% and the sensitivity is 99.9% with a 95% confidence level of 98.7–100%.

Subjects classified as Toxoplasma-negative presented with a mean IgG concentration of .27 IU/mL (\pm .46; max. 1.68) while those classified as Toxoplasma-positive presented with a mean IgG concentration of 152.57 IU/mL (\pm 76.38; min. 23.74).

Table 1

Demographic data and personality/mood scores for the two different groups investigated. Applying *t*-tests (*p* = .05), we did not find significant group differences in any of the reported measures.

	Toxo-negative		Toxo-positive	
	Mean value	SD	Mean value	SD
n	18		18	
Sex	13♂, 5♀		13♂, 5♀	
Age in years	23.83	2.52	25.11	2.62
Height in cm	179.28	8.08	180.28	9.04
Weight in kg	76.44	9.60	79.17	14.50
Alcohol consumption in units/week	3.14	2.41	2.44	2.63
Cigarettes smoked per day	0.89	1.91	0.72	2.28
EHI score	0.93	0.13	0.85	0.18
ASI score	18.06	8.87	14.06	8.52
BDI score	6.78	5.18	3.89	3.00
NEO-FFI score neuroticism	20.72	8.05	16.67	5.63
NEO-FFI score extraversion	28.50	6.26	30.50	5.05



Fig. 1. Illustration of the Stop-Change task used in this study. Simple GO trials end after the first response to the GO1 stimulus (bold). In contrast, SC trials end after the first response to the CHANGE signal (bold). The stop-signal delay (SSD) between the onset of the GO1 stimulus and the STOP signal was adjusted using a staircase procedure described in the methods section. STOP and CHANGE stimuli were always presented simultaneously. As indicated in the upper right corner, the three CHANGE stimuli were associated with one of the three reference lines (see Section 2 for details).

2.5. T. gondii-IgM

According to the instructions of the manufacturer, samples whose absorbance was equal to or exceeded the "cut-off control" were considered reactive for specific IgM-antibodies to *T. gondii*. Samples with absorbance values below the cut-off value were considered non-reactive for IgM. Borderline concentrations of IgM ranging within $\pm 10\%$ of the cut-off value were retested. The diagnostic specificity of the IgM-test is 99.3% with a 95% confidence level of 98.0–99.9% and the sensitivity is 99.4% with a 95% confidence level of 99.3–100%. Subjects classified as Toxoplasmapositive by means of IgG antibody concentration presented with a mean IgM concentration of .36 IU/mL (\pm .26).

2.6. Setting and task

Stimuli were presented on a 17 inch CRT computer monitor and via headphones in a dimly lit and sound-attenuated room. Responses were recorded using four buttons located on two different custom-made response panels placed in front of the participants. Presentation (version 14.9. by Neurobehavioral Systems, Inc.) was used for stimulus presentation and response recording.

The task was a modified version of a stop-change paradigm by Verbruggen et al. (2008) and is illustrated in Fig. 1. Before the start of the experiment, each participant completed an extensive exercise (duration of approx. 10-15 min) which explained the task demands step by step and provided the possibility to practice the task. Before the start of the experiment, all participants included in this study stated to understand the task and to feel capable of performing it. The experiment consisted of 720 trials (divided into 6 blocks) and took the participants approx. 30 min to finish. Throughout every trial, a rectangle $(20 \times 96 \text{ mm})$ containing four vertically aligned circles (8 mm diameter) and three horizontal reference lines (line thickness: 1 mm, width: 8 mm) separating the circles were presented on a black background on the screen. At the start of each trial, all lines were white and the four circles were filled with black color. After 250 ms, one of the circles was filled with white color thus becoming the GO1 target stimulus.

The experiment consisted of two conditions: In the GO1 condition (80% of trials), the participants' response was expected to indicate whether this filled white circle (target) was located above or below the middle reference line. Responses were given by pressing the outer right key with the right middle finger ("above" judgment) or by pressing the inner right key with the right index finger ("below" judgment). All stimuli remained visible until the participant either responded or 2500 ms had elapsed. In case of reaction times (RTs) longer than 1000 ms the German word "Schneller!" (which translates to "Faster!") was presented above the box until the participant responded and thereby ended the trial.

The remaining 20% of trials were stop-change (SC) trials. Like the GO1 condition, the SC condition started with the presentation of a white GO1 stimulus. After a variable 'stop-signal delay' (SSD), a STOP signal (a red rectangle replacing the usual white frame; depicted grey in Fig. 1) was presented, putting an end to the GO1 trial. This STOP signal remained on the screen until the end of the trial and requested the participant to try to inhibit the right hand response to the GO1 stimulus whenever possible. The SSD was initially set to 450 ms and adapted to the participants' performance by means of a 'staircase procedure' (see Verbruggen et al., 2008) yielding a 50% probability of successfully inhibited GO1 responses.

Irrespective of the inhibition performance, every stop signal was combined with one of three possible CHANGE stimuli. The CHANGE stimulus was a 100 ms sine tone presented via headphones at 75 dB SPL and was either high (1300 Hz), medium (900 Hz) or low (500 Hz). It assigned a new reference line in relation to which the GO2 stimulus (the previous GO1 white target circle that had remained on the screen during the whole trial) had to be judged. While the high tone implemented the highest of the three lines as the new reference, the medium tone coded for the middle line and the low tone coded for the lowest line (see Fig. 1). All three reference lines were in effect equally often. The required GO2 response had to be performed with the left hand. If the target circle was located above the newly assigned reference line, an outer left key press (left middle finger) was required and if target circle was located below the newly assigned reference line, a left inner key press (left index finger) was required. In all SC trials, the STOP and CHANGE stimuli were presented simultaneously. In case of RTs longer than 2000 ms the German word "Schneller!" (which translates to "Faster!") was presented above the box until the participant responded to end the trial.

After each SC trial, the staircase algorithm adjusted the SSD that was used in the subsequent SC trial (Logan and Cowan, 1984). In case of a completely correct SC trial (no response to GO1 stimulus,

no response before the GO2 stimulus in SCD300 conditions and a correct left hand response to the GO2 stimulus), the SSD was adjusted by adding 50 ms to the SSD of the evaluated trial. In case of an erroneous SC trial (if any of the above criteria were not met), the SSD was adjusted by subtracting 50 ms from the SSD of the evaluated trial. Limiting this procedure, SSD values were set not to deceed a value of 50 ms and not to exceed a value of 1000 ms.

During the inter-trial interval (ITI, fixed duration of 900 ms), a fixation cross was presented in the center of the screen. Participants were instructed to respond as fast and accurately as possible. Each of the six blocks contained the same number of trials per condition which were presented in a pseudo-randomized order that had been created using the Matlab randomization function (applying no additional randomization criteria).

2.7. EEG data recording and processing

While the participants were performing the task, an EEG was recorded from 65 Ag-AgCl electrodes at standard positions (international 10-20 system). Data preprocessing steps were similar to those described by Mückschel et al. (2013) and Stock et al. (2013). Electrode FCz was used as the primary reference. Applying a filter bandwidth of 0-80 Hz, EEG data was recorded with a sampling rate of 1000 samples per second. Electrode impedances were kept below 5 k Ω . IIR filtering was applied offline in the band-pass from 0.5 to 18 Hz (using a slope of 48 dB/oct). Data sets were visually inspected and all segments contaminated by technical artifacts were rejected. An independent component analysis (ICA) applying the infomax algorithm was used to remove horizontal and vertical eye movements and pulse artifacts from the unepoched data sets. For the analysis of response-locked event-related potentials (ERPs), segments were formed for the SC trials. Epochs started 2000 ms before the simultaneously presented STOP/CHANGE stimulus (set to time point zero) and ended 2000 ms after the stimulus, resulting in an epoch length of 4000 ms. Only trials that had been correctly answered within the first 2000 ms after the onset of the stimulus presentation were included. An automated artifact rejection procedure was run using a maximum voltage step of more than 50 μ V/ ms, a maximal value difference of 200 μ V in a 200 ms interval, or activity below 0.5 µV as rejection criteria. To re-reference the data, a current source density (CSD) transformation was applied. The resulting CSD values are given in $\mu V/m^2$. The baseline correction was referred to -900 ms till -700 ms (before the stimulus) to eliminate background activity. The epochs were then averaged.

Based on previous papers investigating a very similar task in healthy young adults (Mückschel et al., 2013; Stock et al., 2013), we decided to quantify the N1 and the P3 components. The N1 component is a measure of attentional stimulus processing (Di Russo et al., 2003; Herrmann and Knight, 2001; Martínez et al., 2006). Based on scalp topography, the N1 component was quantified at electrodes O1 and O2. For this purpose, a peak-to-peak amplitude value was calculated by subtracting the mean amplitude of the N1 peak (150 ms to 250 post-stimulus) from the mean amplitude of the positive pre-stimulus peak (-100-0 ms). The P3 component is of special interest in the context of the stop-change task because it reflects a link between stimulus evaluation and response selection (Falkenstein et al., 1994a,b; Polich, 2007; Verleger, 1988; Verleger et al., 2005) and is modulated by dopamine (Kok et al., 2004; O'Connell et al., 2009; Ratsma et al., 2001; Stock et al., 2013). Based on scalp topography and group differences, the P3 component was quantified at electrode Pz determining the mean activity in the interval of 250-500 ms post-stimulus. The program BrainVision Analyzer (version 2.0.1.5528) was used for the transformations described above.

2.8. Statistical analysis

Behavioral data (RTs and number of hits) were analyzed with the help of repeated-measures analyses of variance (ANOVA). Condition (Go vs. SC) was used as a within-subjects factor and toxoplasmosis (negative vs. positive for antibodies) was used as a between-subjects factor. The peak-to-peak N1 values of the SC condition were analyzed using a repeated-measures ANOVA with the between-subjects factor toxoplasmosis and the within-subjects factor electrode (O1 vs. O2). The P3 component at electrode Pz in SC trials was analyzed using a oneway ANOVA. Greenhouse-Geisser-correction was used whenever necessary. All p-levels for post hoc tests were adjusted using sequential Bonferroni correction (based on the respective number of post hoc tests conducted per ANOVA). Effect sizes were given as the proportion of variance accounted for (η^2) . As a measure of variability, the standard error of the mean (SEM) together with the mean values were given. IBM SPSS statistics 20 was used for all statistical analyses.

3. Results

We examined action cascading using a stop-change paradigm. In short, the paradigm comprises a simple response task (GO) which has to be interrupted and immediately replaced by an alternate reaction in some of the trials (SC). Based on the concentration of IgG and IgM antibodies in their sera, the participants were classified as either Toxoplasma-negative or having a latent *T. gondii* infection ("positive").

3.1. Behavioral results

Their reaction times (RTs) to the two conditions (withinsubjects factor: GO vs. SC trials) were contrasted across groups (between-subjects factor "Toxoplasma": Toxoplasma-positive vs. Toxoplasma-negative). The ANOVA of hit RTs revealed a main effect of condition (F(1,34) = 379.430, p < .001; $\eta^2 = .918$) as well as significant interaction of condition and toxoplasmosis а $(F(1,34) = 11.636, p = .002; \eta^2 = .225)$ (see Fig. 2). Post hoc *t*-tests revealed that this effect was due to a difference in SC trials (t(34) = 2.792, p = .009) where toxo-negative subjects (1121.47 ms ± 196.64) were slower than toxo-positive (949.78 ms \pm 171.48) subjects. No such difference was observed for GO trials (t(34)=-.386,p = .702), where the RTs of toxo-negative subjects (506.79 ms ± 85.81) resembled those of toxo-positive ones (518.30 ms ± 93.00). In order to rule out the possibility of a speed-accuracy tradeoff, the number of hits was analyzed using an ANOVA. The non-significant results for the interaction of condition and toxoplasmosis $(F(1,34) = .559, p = .460; \eta^2 = .016)$ further substantiated the advantage of the Toxoplasma-positive subjects.

3.2. Neurophysiological results

To determine which cognitive subprocess mediates this behavioral effect, we analyzed electrophysiological data (EEG) by quantifying event related potentials (ERPs) in the SC condition. The P3 component was quantified stimulus-locked at electrode Pz using mean amplitude values. A one-way ANOVA showed that toxo-negative subjects had higher amplitude values (10.31 μ V/m² ± 8.86) than toxo-positive (4.62 μ V/m² ± 6.38) subjects (*F*(1,34) = 4.896, *p* = .034, η^2 = .126). (for illustration of results, see Fig. 2).

We also quantified the N1 component. There was no significant difference between groups as shown by the non-significant interaction of electrode and toxoplasmosis (F(1,34) = .136, p = .714, $\eta^2 = .004$).



Fig. 2. Results for correct responses. (A) RTs of correct responses differed only in the SC condition, where subjects with latent *T. gondii* infection (toxoplasma-positive) had significantly faster RTs than their non-infected counterparts. (B) For SC trials answered correctly, the P3 component at electrode P2 differed significantly between infected and non-infected subjects as marked with an asterisk (stimulus-lox-led to the STOP/CHANGE stimuli.)

4. Discussion

All in all, our findings suggest that in healthy young humans, latent *T. gondii* infection provides a benefit in situations that demand the interruption of an ongoing action and subsequent immediate shifting to another alternative. Based on the P3 component differences, this specific advantage is due to a more efficient link between stimulus processing and response selection (Mückschel et al., 2013; Verleger et al., 2005). Given that effect sizes were smaller for the P3 than for the RT measures, it needs however to be noted that this explanation can only account for a proportion of the observed behavioral differences. In contrast to this, attentional processes (measured via the N1 component) are very unlikely to have contributed to the difference between Toxoplasma-negative and -positive subjects. Furthermore, we observed no effect of toxoplasmosis on simple reaction tasks.

The most likely cause for this selective improvement in action cascading is the up-regulation of dopamine which has been shown to eminently modulate the process of switching from one response option to another (Aarts et al., 2010; Avila et al., 2012; Cools et al., 2001; Garcia-Garcia et al., 2010; Humphries et al., 2006; Redgrave et al., 1999). It needs to be noted that we measured cognitive functions modulated by dopamine (and did not directly quantify cerebral dopaminergic neurotransmission) which poses a possible limitation to the interpretation of the data regarding causality effects. Yet, it is very likely that the Toxoplasma-positive participants in this study were subject to an increase in dopamine since *T. gon-dii* can infect most mammals and replicate within a number of nucleated cells, including neurons (Halonen et al., 1996) where it always takes the same course of action (the secretion of tyrosine hydroxylase that ultimately leads to an increase in dopamine

production and release in catecholaminergic neurons (Gaskell et al., 2009; McConkey et al., 2013; Prandovszky et al., 2011; Webster et al., 2013)). This increase in dopamine has repeatedly been correlated with a heightened risk for certain psychiatric diseases like schizophrenia, suicide and workplace accidents (Flegr, 2013; Webster et al., 2013). Yet, the discrepancy between prevalence rates of latent *T. gondii* infection and psychiatric diseases strongly suggests that most infected humans do not seem to display overt pathological changes in cognition and behavior so that until recently, latent *T. gondii* infection has been considered to be rather asymptomatic in most humans (Flegr, 2013; Kamerkar and Davis, 2012).

In the light of this background, our findings suggest that things lie differently: Rather than leading to pathological changes in a small number of the infected individuals and leaving the rest unaffected, latent *T. gondii* infection seems to trigger (subtle) changes in all infected individuals. For a few individuals, the up-regulation of dopaminergic signaling seems to be the proverbial "straw that breaks the camel's back" which pushes them over the threshold for multifactorial pathological consequences like schizophrenia. This, however, does not apply to the vast majority of infected humans who instead seem to experience an improvement in action cascading processes (as a subset of executive control functions) in the absence of overt pathological consequences.

Furthermore, it can be assumed that all dopaminergic pathways are subject to similar changes (McConkey et al., 2013). Hence, we expect other dopamine-modulated cognitive functions like error detection (Beste et al., 2008, 2009, 2010a,b) and conflict monitoring (Willemssen et al., 2009) to be subtly altered as well. Yet, we need to acknowledge that despite strong evidence for this assumption, further and more direct proof/measurement of heightened dopamine levels in all latently infected humans is needed to prove a direct conjecture between *T. gondii* infection, dopamine and behavior. Also, no simple general prediction on its effects can be made because dopamine seems to modulate executive functions in the fashion of an inverted U-shaped curve (Goldman-Rakic et al., 2000; Seamans and Yang, 2004) and *T. gondii* is by far not the only factor influencing cerebral dopamine levels.

5. Conclusions

Summing up our findings, individuals with latent toxoplasmosis display an improvement in action control which contradicts the commonly held view that parasitic manipulation is always to the detriment of the host. A potential explanation for this contradiction is provided by the fact that humans are dead-end hosts to the parasite so that no direct negative consequences (like predation) arise from dopamine-triggered changes in action control (or exploratory behavior). Given the high prevalence rates of human *T. gondii* infection and our finding that some aspects of human behavior are effectively altered by latent *T. gondii* infection, we consider our findings to be important to a vast number of research topics evolving around the role of dopamine for human cognition and behavior.

Acknowledgment

This work was supported by a grant from Deutsche Forschungsgemeinschaft (DFG) BE4045/10-1 to C.B.

References

Aarts, E., Roelofs, A., Franke, B., Rijpkema, M., Fernández, G., Helmich, R.C., Cools, R., 2010. Striatal dopamine mediates the interface between motivational and cognitive control in humans: evidence from genetic imaging. Neuropsychopharmacology 35, 1943–1951.

- Alonso, R., Chaudieu, I., Diorio, J., Krishnamurthy, A., Quirion, R., Boksa, P., 1993. Interleukin-2 modulates evoked release of [3H]dopamine in rat cultured mesencephalic cells. J. Neurochem. 61, 1284–1290.
- Avila, C., Garbin, G., Sanjuán, A., Forn, C., Barrós-Loscertales, A., Bustamante, J.C., Rodríguez-Pujadas, A., Belloch, V., Parcet, M.A., 2012. Frontostriatal response to set switching is moderated by reward sensitivity. Soc. Cogn. Affect. Neurosci. 7, 423–430.
- Barnes, J.J.M., Dean, A.J., Nandam, L.S., O'Connell, R.G., Bellgrove, M.A., 2011. The molecular genetics of executive function: role of monoamine system genes. Biol. Psychiatry 69, e127–143.
- Berdoy, M., Webster, J.P., Macdonald, D.W., 2000. Fatal attraction in rats infected with *Toxoplasma gondii*. Proc. Biol. Sci. 267, 1591–1594.
- Beste, C., Saft, C., Konrad, C., Andrich, J., Habbel, A., Schepers, I., Jansen, A., Pfleiderer, B., Falkenstein, M., 2008. Levels of error processing in Huntington's disease: a combined study using event-related potentials and voxel-based morphometry. Hum. Brain Mapp. 29, 121–130.
- Beste, C., Willemssen, R., Saft, C., Falkenstein, M., 2009. Error processing in normal aging and in basal ganglia disorders. Neuroscience 159, 143–149.
- Beste, C., Baune, B.T., Domschke, K., Falkenstein, M., Konrad, C., 2010a. Dissociable influences of NR2B-receptor related neural transmission on functions of distinct associative basal ganglia circuits. Neuroimage 52, 309–315.
- Beste, C., Kolev, V., Yordanova, J., Domschke, K., Falkenstein, M., Baune, B.T., Konrad, C., 2010b. The role of the BDNF Val66Met polymorphism for the synchronization of error-specific neural networks. J. Neurosci. 30, 10727– 10733.
- Boothroyd, J.C., Grigg, M.E., 2002. Population biology of *Toxoplasma gondii* and its relevance to human infection: do different strains cause different disease? Curr. Opin. Microbiol. 5, 438–442.
- Chambers, C.D., Garavan, H., Bellgrove, M.A., 2009. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci. Biobehav. Rev. 33, 631–646.
- Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb. Cortex 11, 1136–1143.
- Di Russo, F., Martínez, A., Hillyard, S.A., 2003. Source analysis of event-related cortical activity during visuo-spatial attention. Cereb. Cortex 13, 486–499.
- Eagle, D.M., Baunez, C., 2010. Is there an inhibitory-response-control system in the rat? evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci. Biobehav. Rev. 34, 50–72.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., 1994a. Effects of choice complexity on different subcomponents of the late positive complex of the event-related potential. Electroencephalogr. Clin. Neurophysiol. 92, 148–160.
- Falkenstein, Michael., Hohnsbein, J., Hoormann, J., 1994b. Time pressure effect on
- late components of the event-related potential (ERP). J. Psychophysiol. 8, 22–30. Flegr, J., 2013. How and why Toxoplasma makes us crazy. Trends Parasitol. 29, 156– 163.
- Garcia-Garcia, M., Barceló, F., Clemente, I.C., Escera, C., 2010. The role of the dopamine transporter DAT1 genotype on the neural correlates of cognitive flexibility. Eur. J. Neurosci. 31, 754–760.
- Gaskell, E.A., Smith, J.E., Pinney, J.W., Westhead, D.R., McConkey, G.A., 2009. A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. PLoS ONE 4, e4801.
- Goldman-Rakic, P.S., Muly 3rd, E.C., Williams, G.V., 2000. D(1) receptors in prefrontal cells and circuits. Brain Res. Brain Res. Rev. 31, 295–301.
- Halonen, S.K., Lyman, W.D., Chiu, F.C., 1996. Growth and development of *Toxoplasma gondii* in human neurons and astrocytes. J. Neuropathol. Exp. Neurol. 55, 1150–1156.
- Henriquez, S.A., Brett, R., Alexander, J., Pratt, J., Roberts, C.W., 2009. Neuropsychiatric disease and *Toxoplasma gondii* infection. NeuroImmunoModulation 16, 122–133.
- Herrmann, C.S., Knight, R.T., 2001. Mechanisms of human attention: event-related potentials and oscillations. Neurosci. Biobehav. Rev. 25, 465–476.
- Humphries, M.D., Stewart, R.D., Gurney, K.N., 2006. A physiologically plausible model of action selection and oscillatory activity in the basal ganglia. J. Neurosci. 26, 12921–12942.
- Jones-Brando, L., Torrey, E.F., Yolken, R., 2003. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of *Toxoplasma gondii*. Schizophr. Res. 62, 237–244.
- Kamerkar, S., Davis, P.H., 2012. Toxoplasma on the brain: understanding host-pathogen interactions in chronic CNS infection. J. Parasitol. Res. 2012, 589295.
- Kok, A., Ramautar, J.R., De Ruiter, M.B., Band, G.P.H., Ridderinkhof, K.R., 2004. ERP components associated with successful and unsuccessful stopping in a stopsignal task. Psychophysiology 41, 9–20.
- Logan, G.D., Cowan, W.B., 1984. On the ability to inhibit thought and action: a theory of an act of control. Psychol. Rev. 91, 295–327.
- Martínez, A., Teder-Sälejärvi, W., Vazquez, M., Molholm, S., Foxe, J.J., Javitt, D.C., Di Russo, F., Worden, M.S., Hillyard, S.A., 2006. Objects are highlighted by spatial attention. J. Cogn. Neurosci. 18, 298–310.

- McConkey, G.A., Martin, H.L., Bristow, G.C., Webster, J.P., 2013. Toxoplasma gondii infection and behaviour – location, location, location? J. Exp. Biol. 216, 113–119.
 Moore, J., 1984. Altered behavioural responses in intermediate hosts – an
- acanthoceptalan parasite strategy. Am. Nat. 123, 572–577. Mückschel, M., Stock, A.-K., Beste, C., 2013. Psychophysiological mechanisms of
- interindividual differences in goal activation modes during action cascading. Cereb. Cortex. http://dx.doi.org/10.1093/cercor/bht066 [Epub ahead of print].
- O'Connell, R.G., Dockree, P.M., Bellgrove, M.A., Turin, A., Ward, S., Foxe, J.J., Robertson, I.H., 2009. Two types of action error: electrophysiological evidence for separable inhibitory and sustained attention neural mechanisms producing error on go/no-go tasks. J. Cogn. Neurosci. 21, 93–104.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
- Petitto, J.M., McCarthy, D.B., Rinker, C.M., Huang, Z., Getty, T., 1997. Modulation of behavioral and neurochemical measures of forebrain dopamine function in mice by species-specific interleukin-2. J. Neuroimmunol. 73, 183–190.
- Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148.
- Prandovszky, E., Gaskell, E., Martin, H., Dubey, J.P., Webster, J.P., McConkey, G.A., 2011. The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. PLoS ONE 6, e23866.
- Ratsma, J.E., van der Stelt, O., Schoffelmeer, A.N., Westerveld And, A., Boudewijn Gunning, W., 2001. P3 event-related potential, dopamine D2 receptor A1 allele, and sensation-seeking in adult children of alcoholics. Alcohol. Clin. Exp. Res. 25, 960–967.
- Ravizza, S.M., Goudreau, J., Delgado, M.R., Ruiz, S., 2012. Executive function in Parkinson's disease: contributions of the dorsal frontostriatal pathways to action and motivation. Cogn. Affect. Behav. Neurosci. 12, 193–206.
- Redgrave, P., Prescott, T.J., Gurney, K., 1999. The basal ganglia: a vertebrate solution to the selection problem? Neuroscience 89, 1009–1023.
- Robbins, T.W., Arnsten, A.F.T., 2009. The neuropsychopharmacology of frontoexecutive function: monoaminergic modulation. Annu. Rev. Neurosci. 32, 267– 287.
- Robert-Gangneux, F., Dardé, M.-L., 2012. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin. Microbiol. Rev. 25, 264–296.
- Schulz, S., Arning, L., Pinnow, M., Wascher, E., Epplen, J.T., Beste, C., 2012. When control fails: influence of the prefrontal but not striatal dopaminergic system on behavioural flexibility in a change detection task. Neuropharmacology 62, 1028–1033.
- Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1–58.
- Skallová, A., Kodym, P., Frynta, D., Flegr, J., 2006. The role of dopamine in Toxoplasma-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology 133, 525–535.
- Stock, A.-K., Blaszkewicz, M., Beste, C., 2013. Effects of binge drinking on action cascading processes: an EEG study. Arch. Toxicol. http://dx.doi.org/10.1007/ s00204-013-1109-2 [Epub ahead of print].
- Tenter, A.M., Heckeroth, A.R., Weiss, L.M., 2000. Toxoplasma gondii: from animals to humans. Int. J. Parasitol. 30, 1217–1258.
- Treuer, T., Martenyi, F., Karagianis, J., 2007. Parasitosis, dopaminergic modulation and metabolic disturbances in schizophrenia: evolution of a hypothesis. Neuro Endocrinol. Lett. 28, 535–540.
- Van Holstein, M., Aarts, E., van der Schaaf, M.E., Geurts, D.E.M., Verkes, R.J., Franke, B., van Schouwenburg, M.R., Cools, R., 2011. Human cognitive flexibility depends on dopamine D2 receptor signaling. Psychopharmacology 218, 567– 578.
- Verbruggen, F., Schneider, D.W., Logan, G.D., 2008. How to stop and change a response: the role of goal activation in multitasking. J. Exp. Psychol. Hum. Percept. Perform. 34, 1212–1228.
- Verleger, R., 1988. The true P3 is hard to see: some comments on Kok's (1986) paper on degraded stimuli. Biol. Psychol. 27, 45–50.
- Verleger, R., Jaškowski, P., Wascher, E., 2005. Evidence for an integrative role of P3b in linking reaction to perception. J. Psychophysiol. 19, 165–181.
- Vyas, A., Kim, S.-K., Giacomini, N., Boothroyd, J.C., Sapolsky, R.M., 2007. Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. Proc. Natl. Acad. Sci. USA 104, 6442–6447.
- Webster, J.P., 2001. Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour. Microbes Infect. Inst. Pasteur 3, 1037–1045.
- Webster, J.P., 2007. The effect of *Toxoplasma gondii* on animal behavior: playing cat and mouse. Schizophr. Bull. 33, 752–756.
- Webster, J.P., Kaushik, M., Bristow, G.C., McConkey, G.A., 2013. Toxoplasma gondii infection, from predation to schizophrenia: can animal behaviour help us understand human behaviour? J. Exp. Biol. 216, 99–112.
- Webster, J.P., Lamberton, P.H.L., Donnelly, C.A., Torrey, E.F., 2006. Parasites as causative agents of human affective disorders? the impact of anti-psychotic, mood-stabilizer and anti-parasite medication on *Toxoplasma gondii's* ability to alter host behaviour. Proc. Biol. Sci. 273, 1023–1030.
- Willemssen, R., Müller, T., Schwarz, M., Falkenstein, M., Beste, C., 2009. Response monitoring in de novo patients with Parkinson's disease. PLoS ONE 4, e4898.