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The Role of Dopamine in Planning

Verfasserin:

Nele-Sophie Motzki BSc

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Betreuer:	Ass.-Prof. Dr. Christoph Eisenegger

Zusammenfassung

Planen, welches eine wichtige kognitive Fertigkeit darstellt, wurde in der Vergangenheit mehrfach mit dem Neurotransmitter Dopamin in Zusammenhang gebracht. Da vorherige Studien, in Bezug auf die Richtung dieses Zusammenhangs, zu unterschiedlichen Ergebnissen gelangt sind bedarf dieses Thema weiterer Forschung. In der vorliegenden Studie wurde der Zusammenhang von Dopamin und Planen in einem Between-Subject, Placebo-kontrollierten Design untersucht. 77 männlichen Teilnehmern wurde entweder eine hohe Dosis des Dopamin D2/D3 Antagonisten Sulpiride (800 mg) oder ein Placebo verabreicht. Zusätzlich wurden alle Teilnehmer im Hinblick auf einen Genpolymorphismus, welcher im Zusammenhang steht mit der striatalen Dichte von Dopamin D2 Rezeptoren, stratifiziert. Die Planungsfähigkeit wurde erhoben mit dem One-Touch Stockings of Cambridge (OTSOC), welches eine modifizierte Version des Tower of London task darstellt. Wie hypothesiert wurde, führte die Verabreichung des Dopamin D2/D3 Antagonisten Sulpiride zu einer verminderten Leistung in der Planungsaufgabe. Des Weiteren, wurden keine Effekte bezogen auf den Genpolymorphismus gefunden. Dies bedeutet, dass Probanden sich nicht in Abhängigkeit von ihrer striatalen Dopamin D2 Rezeptor Dichte unterschieden. Die Ergebnisse der vorliegenden Studie zeigen die Möglichkeit auf, dass Sulpiride nicht nur an striatalen Dopamin D2/D3 Rezeptoren wirkt, sondern ebenfalls kortikale Dopamin Rezeptoren blockiert. Die vorliegenden Ergebnisse stellen zudem die prominente Rolle striataler Dopamin D2 Rezeptoren in Frage. In zukünftigen Studien, sollte eine mögliche wichtige Rolle von Dopamin D3 Rezeptoren, beim Planen untersucht werden.

Abstract

Numerous studies have brought forward evidence for a prominent role of dopamine in planning. Because the direction of the effect of dopamine in planning is ambiguous this issue is in need of further investigation. In this between-subject, placebo-controlled study, administration of high doses (800 mg) of the dopamine D2/D3 antagonist sulpiride was combined with genetic analysis of the striatal dopamine D2 receptor. The One-Touch Stockings of Cambridge (OTSOC), a modified version of the original Tower of London task was used to measure planning in a sample of 77 healthy male volunteers. As hypothesized we found impaired planning performance at the OTSOC following sulpiride administration. We did not find modulatory effects concerning striatal dopamine D2 receptor density. Our findings suggest that sulpiride might not predominantly act on striatal dopamine D2/D3. The exhibited sulpiride effect could also be the consequence of cortical dopamine D2/D3 receptor blockade. Furthermore, our findings question the proposed prominent role of dopamine D2 receptors in planning. Hence a possible crucial role of dopamine D3 receptors in planning should be investigated in future studies.

Contents

The Role of Dopamine in Planning

In our daily lives we are often confronted with problems which require planning, the ability to model and anticipate consequences of actions prior to their actual executions in the real world (Goel & Grafman, 1995). People with proficient planning abilities are adapted to our environment in a better way. Cognitive planning abilities can be investigated experimentally using the Tower of London (TOL) task (Shallice, 1982). In this task, subjects are asked to mimic a display of three colored balls arranged within three stockings. In doing so, it is required to preplan mentally the sequence of moves needed to match the goal state before executing the moves (Goel & Grafman, 1995). Successful performance in the TOL task is known to be a function of working memory capacity (Owen, Doyon, Petrides, & Evans, 1996). Working memory is required in the search process for the correct solution in which several subsequences are mentally rehearsed and either accepted or rejected. If accepted, those subsequences are stored into working memory until the total sequence of moves needed to solve the problem is encountered (Owen, 1997). The TOL task assesses two fundamental parameters, the number of attempts made to correctly solve the task (accuracy) as well as the time taken to think of the correct solution (latency) (Shallice, 1982).

Planning abilities have so far been linked primarily to functioning in the prefrontal cortex (Goel & Grafman, 1995; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Shallice, 1982). For instance, patients with unilateral or bilateral frontal lobe excisions showed profound impairment in solving the TOL task (Owen et al., 1990). Further, impaired planning has also been observed in patients suffering from neurodegenerative disorders that affect the basal ganglia such as Parkinson disease (PD) or Huntington disease (HD) (Lawrence et al., 1998b; Morris, Sahakian, Evenden, Heald & Robbinsii, 1988; Owen, Sahakian, Summers, Robbins, Hodges & Polkey 1995; Pavese et al., 2003). Performing the TOL task PD patients showed both impaired planning accuracy as well as slowed initial thinking time (Morris et al., 1988, Owen et al., 1995). Correspondingly, brain imaging studies brought forward evidence for cortical activation in fronto-parietal regions (Baker et al., 1996; Dagher, Owen, Boecker, & Brooks, 2001; Owen et al., 1996; Rowe, Owen, Johnsrude & Passingham 2001) as well as subcortical activations in the caudate nucleus (Baker et al., 1996; Owen et al., 1996; Rowe et al., 2001) while performing the TOL task. Hence planning seems to be linked to the frontal cortex as well as the striatum. Therefore, cognitive planning abilities are assumed to be mediated by mechanisms within fronto-striatal circuitry (Alexander & Garett, 1986; Middleton & Strick, 1994). The concept of fronto-striatal circuitry emphasizes the functional inter-relationship between the frontal cortex and the striatum. As a result of a circuit between prefrontal cortex and striatum, the output of the striatum can influence cortical higher-order functions

such as planning (Middelton & Strick, 1994). In case of PD patients, disturbed striatal output could be the source of planning impairment (Owen et al., 1995; Sawamoto, Piccini, Hotton, Pavese, Thielemans & Brooks, 2008). It is assumed that the most significant structural damage found in PD patients is located in the dopamine-producing cells of the substantia nigra parscompacta (Paulus & Jellinger, 1991). A following degeneration of the striatal dopamine system could be the reason for a disturbed striatal output, which might lead to the observed planning impairment in this patient group (Sawamoto et al., 2008). In line with this assumption planning performances were modulated following L-Dopa medication withdrawal in PD patients (Lange, Marsden, James, Owen, & Paul, 1992). Thus, patients that were not medicated with L-Dopa were slower in solving a planning task compared with patients that were medicated. Correspondingly, Pavese et al. (2003) put forward evidence for a relation between striatal dopamine D2 receptor loss in HD patients and planning accuracy in the TOL task. They showed that the higher the loss of dopamine D2 receptors, the larger the impairment concerning planning accuracy. Further evidence concerning the role of dopamine in planning in healthy subjects was brought forward by Elliot et al. (1996). They found that methylphenidate which acts as an indirect dopamine agonist enhanced planning performances at the TOL task. Summarizing the outlined above, dopamine reduction seems to be linked to planning impairment whereas dopamine enhancement seems to be linked to planning improvement.

Contradicting this notion, Mehta, McGowan, Lawrence, Aitken, Montgomery and Grasby (2003) found reversed effects of dopamine on planning performances using the dopamine D2/D3 antagonist sulpiride in a study with healthy volunteers. Their results indicated that sulpiride administration (400 mg) led to better planning performances at the TOL task compared with a placebo group. This result seems to appear at odds given the presented notion that degeneration of the striatal dopamine system in PD patients resulted in planning impairment. One explanation that can account for this result is that a dose of 400 mg sulpiride, which results in an occupancy of roughly 30% of striatal dopamine D2/D3 receptors (Mehta et al., 2003) might not be sufficient to result in cognitive planning impairment. This is in line with the notion that only mildly affected PD patients have no troubles in performing the TOL task (Dagher et al., 2001). In case of mildly affected PD patients the degeneration of the striatal dopamine system might not be that progressed and therefore they have no difficulties in planning (Dagher et al., 2001). Yet, this would not explain the enhancement in planning following sulpiride administration. This pattern of result might be due to specific pharmacological effects of sulpiride. Dopamine D2/D3 receptors are found on post-synaptic neurons and on pre-synaptic neurons where they act as autoreceptors (Möller, 2003). In contrast to post-synaptic receptor blockade, pre-synaptic D2/D3 receptor blockade increases

neuronal release of dopamine (Leucht, 2004; Möller, 2003). Sanger et al. (1999) stated that, low doses of amisulpride (similar to sulpiride, both are selective for Dopamine D2/D3 receptors) preferentially occupy pre-synaptic receptors (as cited in Möller, 2003). Since Mehta et al. (2003) used only low doses of sulpiride (400 mg) their pattern of results observed might be due to predominant pre-synaptic autoreceptor blockade. In that case increased dopamine release following dopamine D2/D3 autoreceptor blockade might have leaded to improved planning performances. Consequently, administration of high doses of sulpiride is needed in order to achieve an effective level of post-synaptic dopamine D2/D3 receptor blockade. In the case of high doses of sulpiride, there is no functional consequence of pre-synaptic antagonism expected (Möller, 2003).

In the present study we administered a dose of 800 mg sulpiride in a group of healthy male participants, resulting in an occupancy of roughly 60% of dopamine D2/D3 receptors (Takano et al., 2006). We expected the group administered with sulpiride to show planning impairment in comparison with the placebo group.

Because there was a strong correlation found between striatal dopamine D2 receptor binding potential and planning in HD patients (Lawrence et al., 1998a), dopamine D2 receptors may possess a prominent role in planning. The minor A1 allele of the Taq1A polymorphism (Thompson et al, 1997, Jönnson et al., 1999) has been associated with a reduction in striatal dopamine D2 receptor density of up to 30% (Jönsson et al., 1999). Therefore A1+ carriers should be more sensitive to dopamine D2 antagonism following sulpiride administration compared with A1- carriers. Therefore we expected subjects genotyped with the A1+ allele to, that received the sulpiride pill to show the most pronounced planning impairment.

Furthermore, it is brought forward that planning performance might be influenced by subjects personal level of impulsivity (Owen, 1997). Concerning cognitive tasks impulsivity displays the preference for speed over accuracy (Phillip and Rabbitt (1995). Perales, Verdejo-García, Moya, Lozano and Pérez-García, (2009) put forward evidence indicating that neurocognitive mechanisms involved in response monitoring and inhibition are linked to impulsivity trait. Including this notion we investigated possible confounding effects of impulsivity trait on planning performances. The UPPS-P impulsivity scale (Cyders, Smith, Spillane, Fischer, Annus & Peterson, 2007) was used to differentiate between low and high impulsive subjects.

In the present study planning was investigated using a modified version of the TOL task, the One-Touch Stocking of Cambridge (OTSOC) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, http://www.camcog.com). In this modified version of the

task, subjects are required to select the minimum number of moves needed to solve the problem without actually moving any of the balls. This modification forces subjects to plan the solution in full before initiating a response. This ensures actual planning and enables the investigation of the specific relation between the time needed to correctly solve the task, the problem difficulty and the accuracy in an improved manner (Cambridge Cognition, http://www.camcog.com).

We hypothesized that the group that received 800 mg of the dopamine D2/D3 antagonist sulpiride should be slower and less accurate in the OTSOC compared with the placebo group. Furthermore, we expected subjects genotyped with the A1+ allele of the Taq1A polymorphism, that received the sulpiride pill to show the most pronounced planning impairment.

Methods

Participants

In total seventy-seven healthy right-handed male volunteers aged between 19 and 44 years (mean = 32.2 ± 7.15) participated in the present study. All participants were European or North American Caucasians, recruited from the Cambridge BioResource panel of volunteers.

Mental and physical health was screened with detailed medical history questionnaires used by the Cambridge BioResource. Plus, a structured interview was performed by the psychiatrist on side. Both inquiries revealed neither a history of neurological disease or psychiatric disorder, nor was any participant taking prescribed medication or gave information about drug abuse of some sort. The present study is in conformity with the Declaration of Helsinki and was approved by the National Research Ethics Committee of Hertfordshire (11/EE/0111). All participants gave informed consent before starting the experiment. In exchange for attendance, all subjects received £50 plus individual additional payment (see Eisenegger et al., 2014). Verbal IQ estimates (mean = 119.8 ± 7.332; range = 101.4 - 129) applying the National Adult Reading Test (Nelson, 1991) as well as full IQ estimates (mean = 119.7 ± 6.61; range = 103.1 - 128) were calculated for all volunteers. Two participants had to be excluded because of troubles in understanding the instructions of the task (placebo group A1-, sulpiride group A1-).

Experimental Design

This study followed a between-subject, double-blind, placebo-controlled design. All seventy-seven participants received a single oral dose of 800 mg sulpiride or a respective placebo in a randomized manner. All participants were stratified based on their dopamine D2 receptor Taq1A genotype, yielding the following four groups: A1+ carriers with sulpiride administration (n = 20) and with placebo administration (n = 17) and A1- carriers with sulpiride administration (n = 19) and with placebo administration (n = 21). There were no differences across groups concerning age (Ps > 0.57), BMI (Ps > 0.227), verbal IQ (Ps > 0.488) or general IQ (Ps > 0.489).

Procedure

On the study day all volunteers arrived at the lab between 8.30 (am) and 10.00 (am). Since participants were not allowed to consume alcohol on the day of the experiment, all volunteers had to undergo an alcohol test before starting (using commercially available breath alcohol analyzer). Subsequently, two questionnaires were used to assess the current mood (VAS) and impulsivity characteristics (UPPS-P). Then, pulse rate and blood pressure were measured and participants gave a

blood sample (10ml) for the first time. Thereafter, all volunteers received either a sulpiride or placebo capsule, which was administered orally. After the ingestion of the pill a waiting period followed in which participants were asked to stay in separate rooms. While waiting volunteers were allowed to read newspapers and served a small snack to increase sulpiride absorption. In line with Mehta et al. (2003), the planning task was administered three hours after capsule ingestion in order to coincide with the time-window of maximal drug effects. Before the task started volunteers had to complete a comprehensive side-effect questionnaire (Rush, Stoops, Hays, Glaser & Hays, 2003) and the current mood, blood pressure and pulse rate was measured and a blood sample was taken for the second time. The OTSOC (Cambridge Cognition, http://www.camcog.com) was presented on computers and responses were registered via touch-sensitive screens. To confirm that participants understood the instructions they had to perform four practice trials before the actual task started. The task consisted of twenty-four problems in total. At the end of the experiment volunteers were asked to guess whether they received the sulpiride or the placebo pill.

CANTAB One-Touch Stockings of Cambridge (OTSOC)

In the task participants were presented with two displays on a computer screen, each showing three colored balls arranged within three stockings. The goal was to mimic the upper display and to achieve this with the least possible number of moves. The difficulty varied from one to six moves needed to solve a problem. Participants were not required to physically move the balls to replicate the upper display but they had to select the minimum number of moves needed from a list of seven possibilities displayed at the bottom of the screen. They were allowed to take as many attempts as needed to solve the problem. The number of attempts (accuracy) and the time taken (ms) to correctly solve the task (latency) were recorded.

Prolactin level assessment

Plasma prolactin level elevation is considered to be an indicator of post-synaptic dopamine receptor antagonism (Meites & Clemens, 1972; Turkington, 1972). According to that notion administration of the dopamine D2/D3 antagonist sulpiride should lead to elevated prolactin levels at the second measure three hours after capsule ingestion (Wiesel, Alfredsson, Ehrnebo & Sedvall, 1982; Wetzel, Wiesner, Hiemke & Benkert, 1994).

Prolactin level was measured using a commercial immunoradiometric assay (MP Biomedicals Ltd, UK). The intra- and inter-assay CVs were 4.2% and 8.2 %, respectively, and the limit of detection was 0.5ng/ml (see Eisenegger et al., 2014).

Impulsivity measures (UPPS-P) & Visual Analogue Scales (VAS)

Impulsivity was assessed using the UPPS-P Impulsive Behavior Scale (Cyders et al. 2007). The UPPS-P is a revised version of the original UPPS created by Whiteside and Lynam (2001). The questionnaire consists of 59 items linked to five sub-scales: negative urgency, positive urgency, (lack of) premeditation, (lack of) perseverance and sensation seeking. Adding the five sub-scales results in a general impulsivity score (Whiteside & Lynam, 2001).

The Visual Analogue Scales (Bond & Lader, 1974) were used to assess participants current mood state. The VAS originally contains sixteen scales. In the present study we investigated alertness, calmness and contentedness.

Statistical analysis

Statistical analysis was performed using the open source software package R. Differences across groups concerning age, BMI, general IQ and verbal IQ were analyzed using t-tests and chi-sqared tests. Concerning the control variables current mood, blood pressure, pulse rate, and prolactin level repeated-measures analysis of variance (ANOVA) were conducted, with time as the within-subject factor and group and genotype as between-subject factors.

Regarding the OTSOC data, to normalize value distribution the latency data was log-transformed and divided by 1000 (Judd, McClelland & Ryan, 1989). Data were subjected to mixed-design ANOVAs since we had two repeated-measure manipulations participant Id and task difficulty level. The between-group variables were genotype, group and impulsivity. In case that Mauchly's test of sphericity indicated that the assumption of sphericity had been violated, the Greenhouse-Geisser corrected *P*-value was interpreted. Bonferroni corrected post-hoc tests were calculated for further investigations of significant main effects or interactions. Significant differences are reported as $P < 0.05$.

Results

One-touch Stockings of Cambridge measures

Performance measures for the OTSOC were accuracy (number of moves needed to solve the task) and latency (time taken to correctly solve the task).

The mean performance data separated over the six task difficulty levels is displayed in Table 1.

Table 1
Summary of OTSOC test results

	Task Difficulty Level					
	1	2	3	4	5	6
Accuracy (mean)						
Sulpiride	0.06 ± 0.52	0.06 ± 0.32	0.18 ± 0.64	0.23 ± 0.63	0.47 ± 0.75	0.74 ± 1.00
Placebo	0.02 ± 0.14	0.05 ± 0.30	0.05 ± 0.24	0.18 ± 0.54	0.31 ± 0.65	0.51 ± 0.81
Latency (mean)						
Sulpiride	1.92 ± 0.83	1.68 ± 0.53	1.85 ± 0.44	2.34 ± 0.63	3.11 ± 0.73	3.30 ± 0.73
Placebo	1.88 ± 0.81	1.64 ± 0.49	1.79 ±0.43	2.33 ± 0.62	3.19 ±0.64	3.55 ± 0.61

Sulpiride (800 mg) effects on the OTSOC planning task. Values shown for each variable are the mean and the standard deviation for each task difficulty level (1-6) separated for the sulpiride and the placebo group. The accuracy score records the number of moves needed to solve the task. An accuracy score of 0 indicates that the first choice was correct. The latency data presented is log-transformed and divided by 1000.

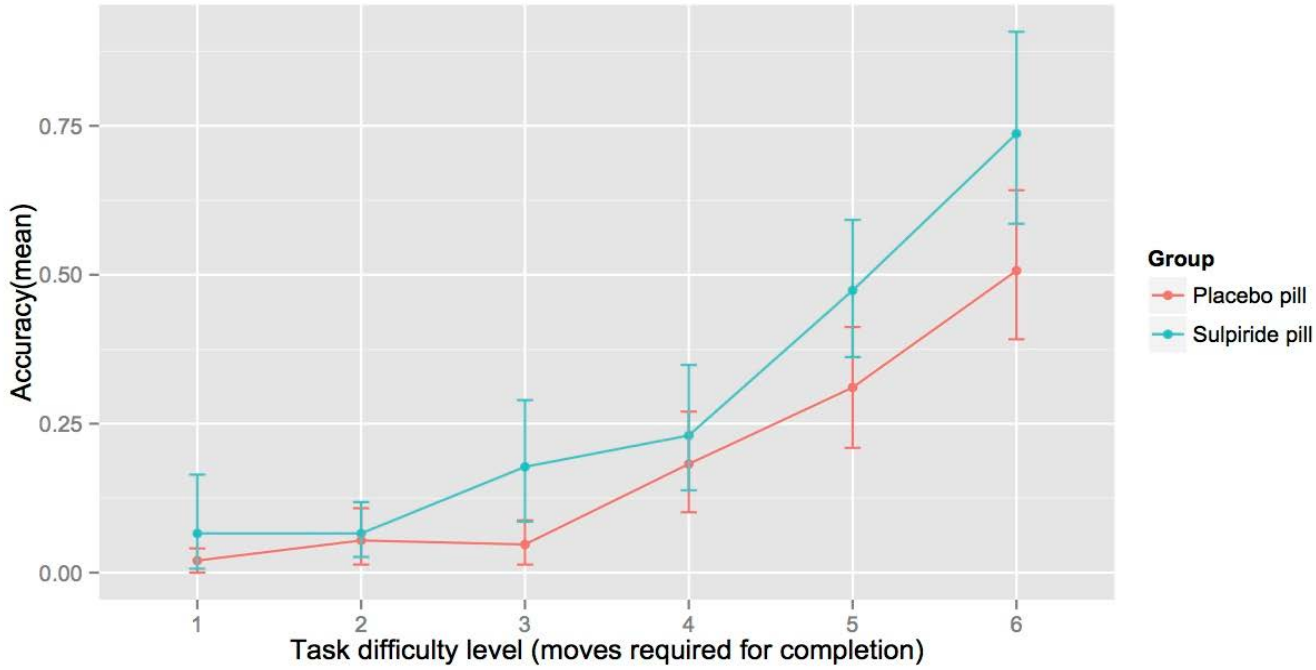
As expected, we found a main effect of task difficulty on accuracy [$F(5,355) = 39.09$, $P < 0.000$]. Post-hoc tests revealed that participants required significantly more attempts to achieve the correct solution for six-move problems compared with all other task difficulty levels ($Ps < 0.000$). Further, there was a significant main effect of group [$F(1,71) = 5.089$, $P = 0.002$] indicating that participants required more attempts to correctly solve the task under the influence of sulpiride displayed in Figure1. Concerning genotype, there was neither a significant main effect [$F(1,71) = 0.005$, $P = 0.94$] nor significant interactions ($Ps > 0.116$) on accuracy. The complete results are displayed in Table 2.

Table 2
Summary of the mixed analysis of variance (accuracy data)

	df (n)	*df* (d)	*F*	*P*	η^2
Group	1	71	5.089	0.027*	0.023
Genotype	1	71	0.005	0.940	< 0.000
Task difficulty level	5	335	30.90	<0.000***	0.271
Group x Genotype	1	71	0.847	0.365	0.003
Group x Task difficulty level	5	335	1.466	0.200	0.013
Genotype x Task difficulty level	5	335	1.574	0.166	0.014
Group x Genotype x Task difficulty level	5	335	0.524	0.757	0.004

*significant codes: 0 '***', 0.001 '**', 0.01 '*', 0.05 '.'

Figure 1 The effects of sulpiride (800mg) on the number of attempts required to correctly solve the OTSOC (accuracy = 0 indicated that the first choice was correct). Means are plotted ± error bars of 2 SD.



For response latencies we also found a main effect of task difficulty [$F(5,355) = 407.2$, $P < 0.000$]. Post-hoc tests indicated that six-move problems took significantly longer to solve compared to all other difficulty levels (*Ps* < 0.000). Further, there was a significant interaction between group and task difficulty level [$F(5,355) = 2.501$, $P = 0.030$]. Because sphericity was violated ($P < 0.000$) and the Greenhouse-Geisser corrected *P*-value was not significant ($P = 0.054$) we interpret this interaction as a trend (Figure 2). Concerning genotype, there was neither a significant main effect [$F(1,71) = 0.300$, $P =$

0.585] nor significant interactions (*P*s > 0.264) on latency. The complete results are displayed in Table 3.

Figure 2 The effects of sulpiride (800mg) on the time taken to correctly solve the OTSOC (latency). Means are plotted ± error bars of 2 SD.

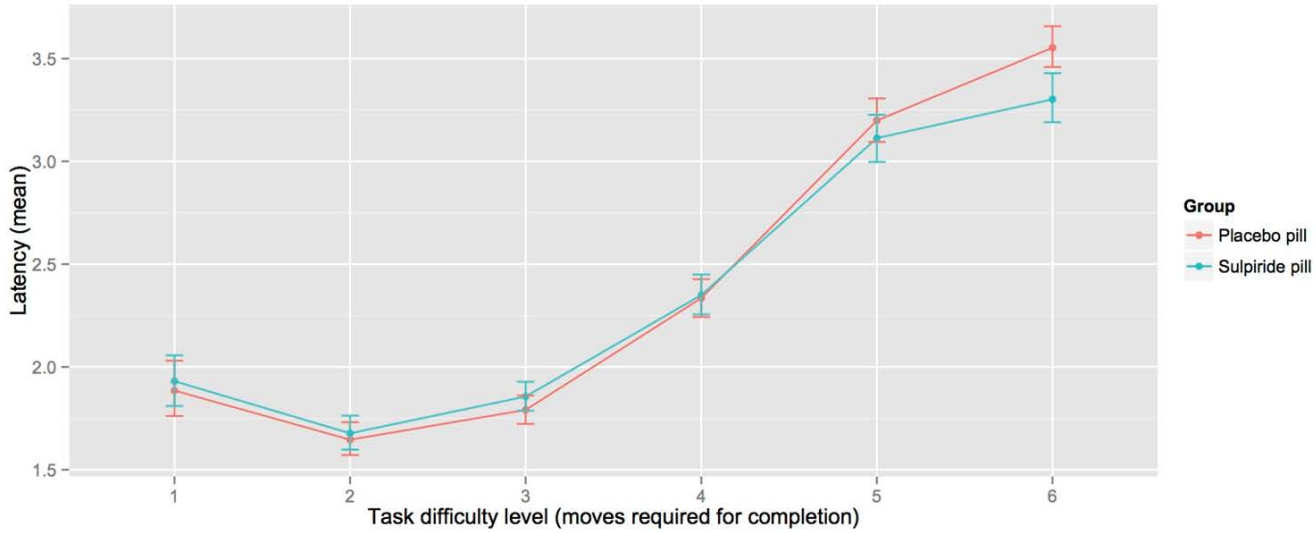


Table 3
Summary of the mixed analysis of variance (latency data)

	df (n)	*df* (d)	*F*	*P*	η^2
Group	1	71	0.349	0.556	0.001
Genotype	1	71	0.300	0.585	0.001
Task difficulty level	5	335	407.2	<0.000***	0.775
Group x Genotype	1	71	0.204	0.652	0.001
Group x Task difficulty level	5	335	2.501	0.031*	0.020
Genotype x Task difficulty level	5	335	1.296	0.264	0.010
Group x Genotype x Task difficulty level	5	335	0.543	0.743	0.004

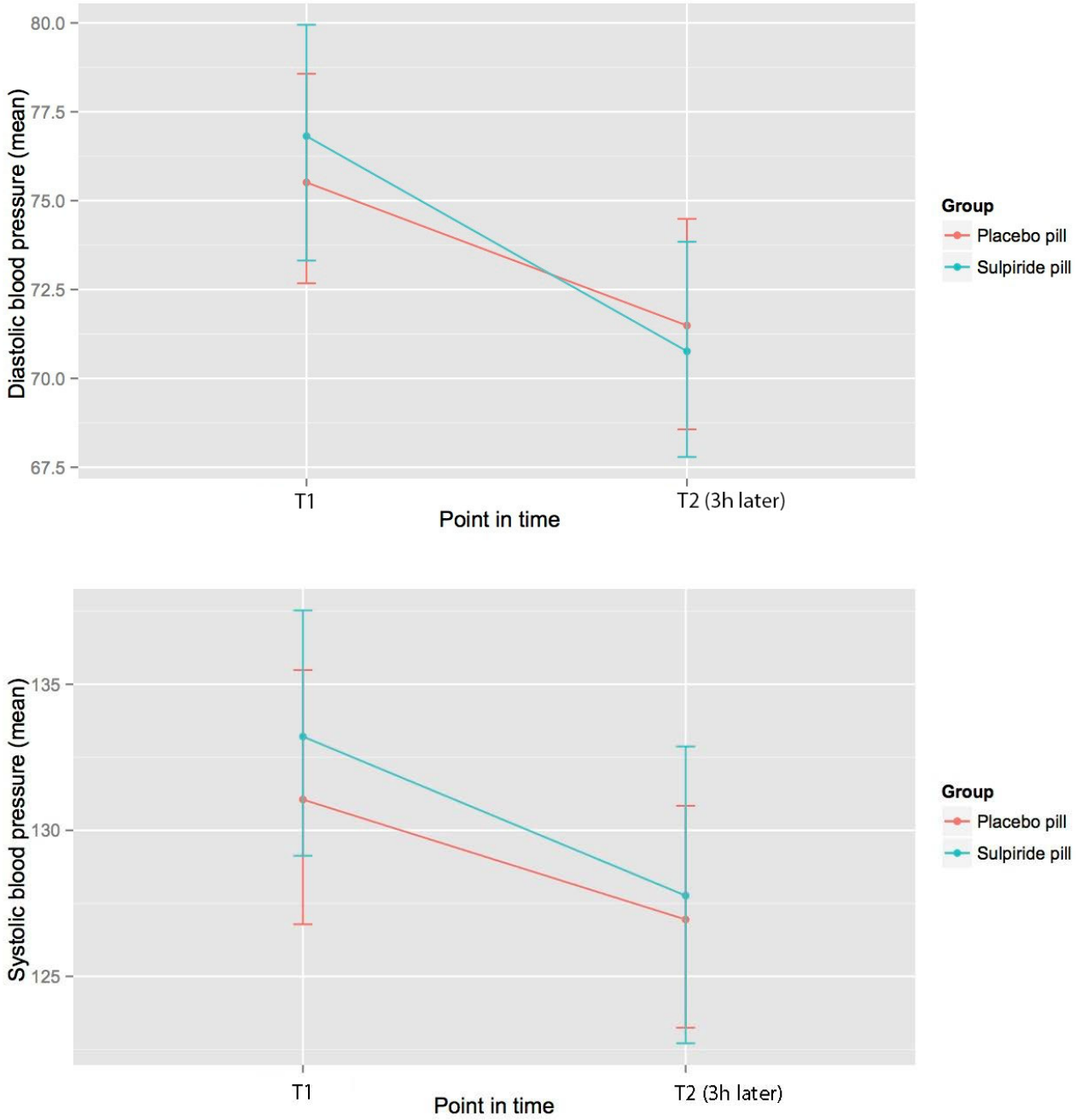
*significant codes: 0 '***', 0.001 '**', 0.01 '*', 0.05 '.'

Physiological measures

Blood pressure There was a main effect of time (baseline versus 3h after capsule ingestion) on blood pressure [diastolic: $F(1,71) = 20.68$, $P = <0.000$; systolic: $F(1,71) = 10.84$, $P <0.001$)] (Figure 3). The (diastolic) blood pressure dropped from 76.1 ± 10.17 (systolic: mean = 132.14 ± 13.29) at baseline

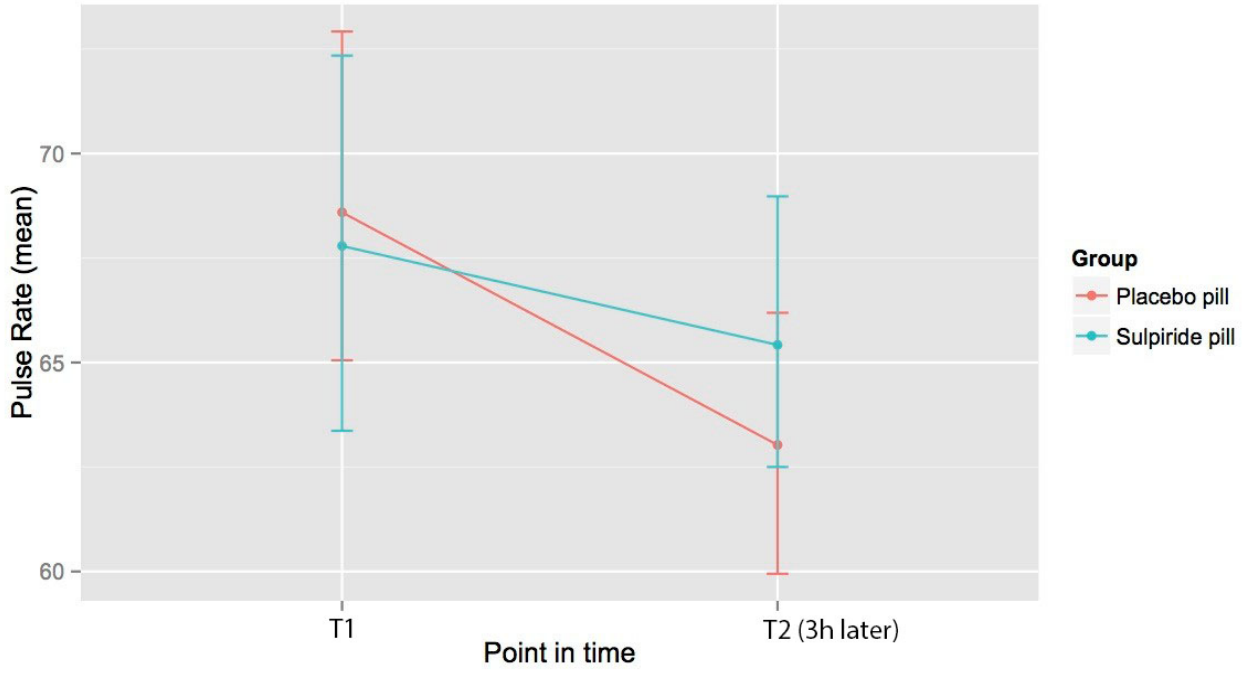
measurement to 71.12 ± 9.98 (systolic: mean = 127.36 ± 13.92) three hours after capsule ingestion. Concerning group there was neither a significant main effect [diastolic: $F(1,71) = 0.003$, $P = 0.98$; systolic: $F(1,71) = 0.27$, $P = 0.604$] nor significant interactions (Ps > 0.33) (see Figure 3). No other main effect or interaction was significant. The complete results are displayed in Table 4.

Figure 3 Means of blood pressure (diastolic, systolic) at baseline measurement (T1) and second measurement, three hours after capsule ingestion (T2). Means are plotted ± error bars of 2 SD.



Pulse rate Concerning pulse rate, we also found a significant main effect of time [F(1,71) = 8.514, *P* = 0.004] (Figure 4). Post-hoc tests revealed that three hours after the capsule ingestion (mean = 64.24 ± 10.01) the pulse rate was significantly lower (*P* = 0.04) compared to the baseline measurement (mean = 68.18 ± 13.11). Concerning group, there was neither a significant main effect [*F*(1,71) = 0.075, *P* = 0.784] nor significant interactions (*P*s > 0.142) (Figure 4). No other main effect or interaction was significant. The complete results are displayed in Table 4.

Figure 4 Pulse rate (means) at baseline measurement (T1) and decond measurement, three hours after capsule ingestion (T2). Means are plotted ± error bars of 2 SD.



Prolactin level measures

Regarding the prolactin level measures, there was a significant main effect of time [*F*(1,68) = 104.6, *P* < 0.000] indicating higher values for the measurement three hours after capsule ingestion. As expected, we found a significant main effect of group [*F*(1,68) = 75.604, *P* < 0.000] displayed in Figure 5. Further, there was a significant interaction between time and group [*F*(1,68) = 114.83, *P* < 0.000] and a trend for an interaction between group and genotype [*F*(1,68) = 3.802, *P* = 0.055]. The complete results are presented in Table 5.

Table 4
Summary of the mixed analysis of variance concerning the physiological control variables: diastolic blood pressure, systolic blood pressure and pulse rate

	df (n)	*df* (d)	*F*	*P*	η^2
Diastolic Blood Pressure:					
Group	1	71	0.003	0.985	<0.000
Genotype	1	71	3.379	0.071	0.035
Time	1	71	0.206	<0.000***	0.062
Group x Genotype	1	71	0.137	0.712	0.001
Group x Time	1	71	0.882	0.350	0.002
Genotype x Time	1	71	0.198	0.657	0.000
Group x Genotype x Time	1	71	0.866	0.355	0.002
Systolic Blood Pressure:					
Group	1	71	0.270	0.604	0.003
Genotype	1	71	0.001	0.966	< 0.000
Time	1	71	10.84	0.001**	0.030
Group x Genotype	1	71	0.712	0.401	0.007
Group x Time	1	71	0.240	0.625	0.000
Genotype x Time	1	71	0.207	0.649	0.000
Group x Genotype x Time	1	71	0.959	0.330	0.002
Pulse Rate:					
Group	1	71	0.075	0.784	0.000
Genotype	1	71	0.978	0.325	0.010
Time	1	71	8.51	0.004**	0.029
Group x Genotype	1	71	2.365	0.128	0.024
Group x Time	1	71	1.429	0.235	0.005
Genotype x Time	1	71	0.056	0.813	0.000
Group x Genotype x Time	1	71	0.242	0.624	0.000

*significant codes: 0 '***', 0.001 '**', 0.01 '*', 0.05 '.'

Figure 5 Prolactin level (means) at baseline (T1) second measurement, three hours after capsule ingestion (T2). Means are plotted ± error bars of 2 SD.

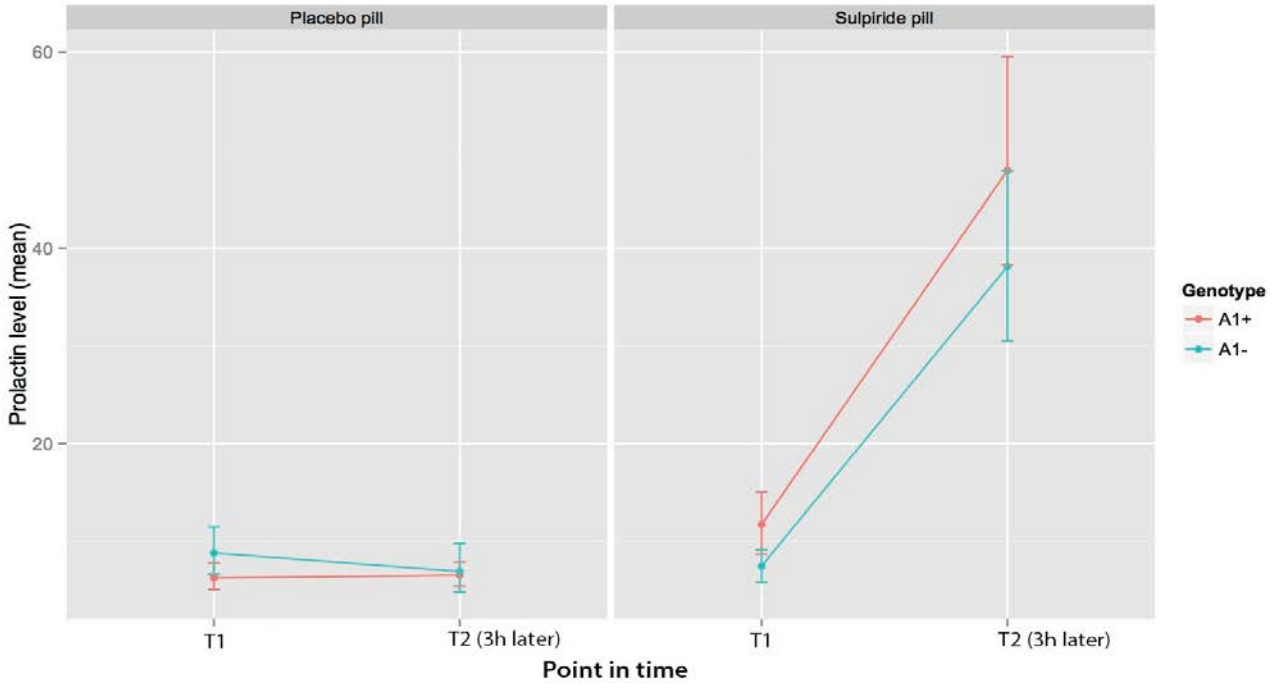


Table 5
Summary of the mixed ANOVA (prolactin level data)

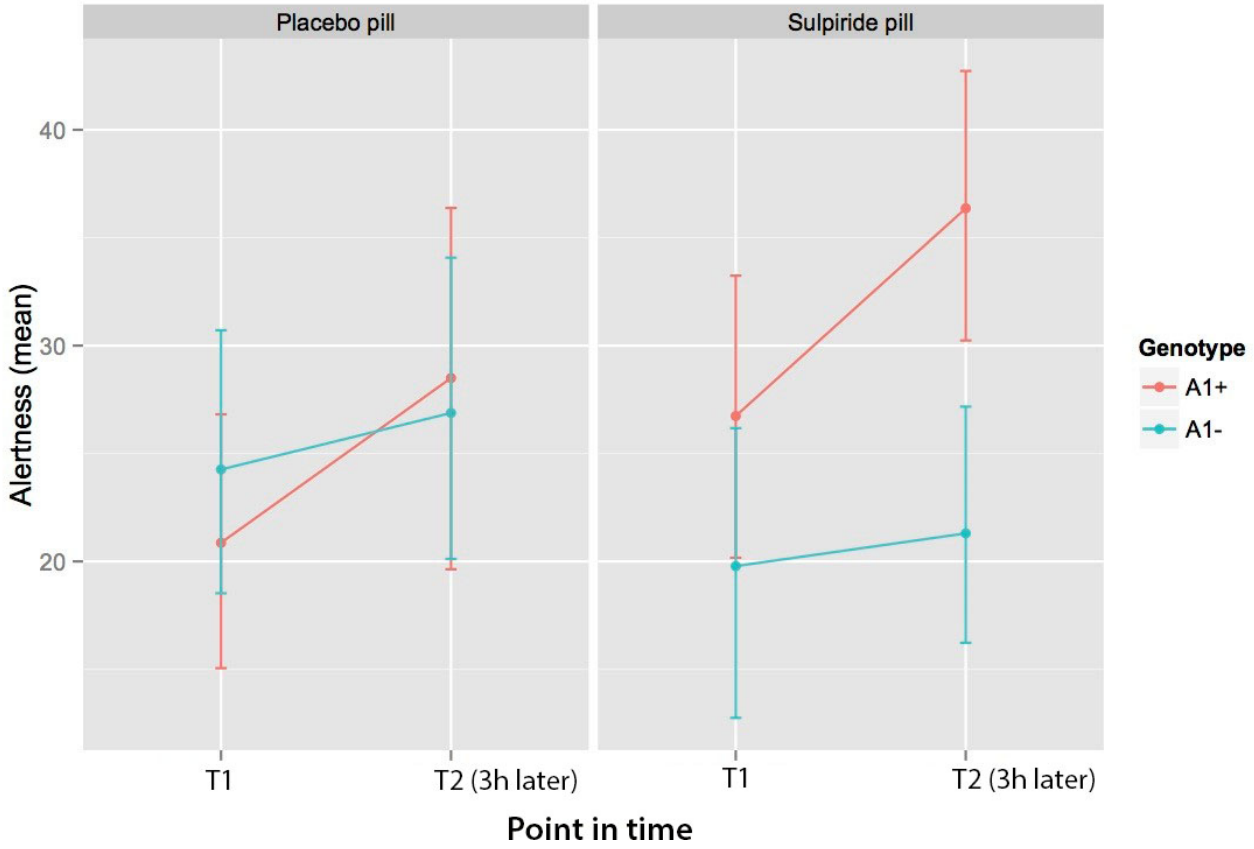
	df (n)	*df* (d)	*F*	*P*	η^2
Group	1	68	75.60	< 0.000***	0.420
Genotype	1	68	1.65	0.203	0.015
Time	1	68	104.6	<0.000***	0.348
Group x Genotype	1	68	3.80	0.055 .	0.035
Group x Time	1	68	114.8	< 0.000***	0.370
Genotype x Time	1	68	1.46	0.229	0.007
Group x Genotype x Time	1	68	0.28	0.595	0.001

significant codes: 0 '*', 0.001 '**', 0.01 '*', 0.05 '.'*

Visual Analogue Scale measures (VAS, Bond & Lader, 1974)

There was a significant main effect of time on alertness [$F(1,70) = 11.338$, $P = 0.0012$] indicating higher values three hours after capsule ingestion ($P = 0.042$). Further, we found a significant interaction between time and genotype [$F(1,70) = 4.33$, $P = 0.041$].). Concerning group, there was neither a significant main effect [$F(1,70) = 0.055$, $P = 0.814$] nor significant interactions (Ps > 0.069) on alertness (see Figure 6).

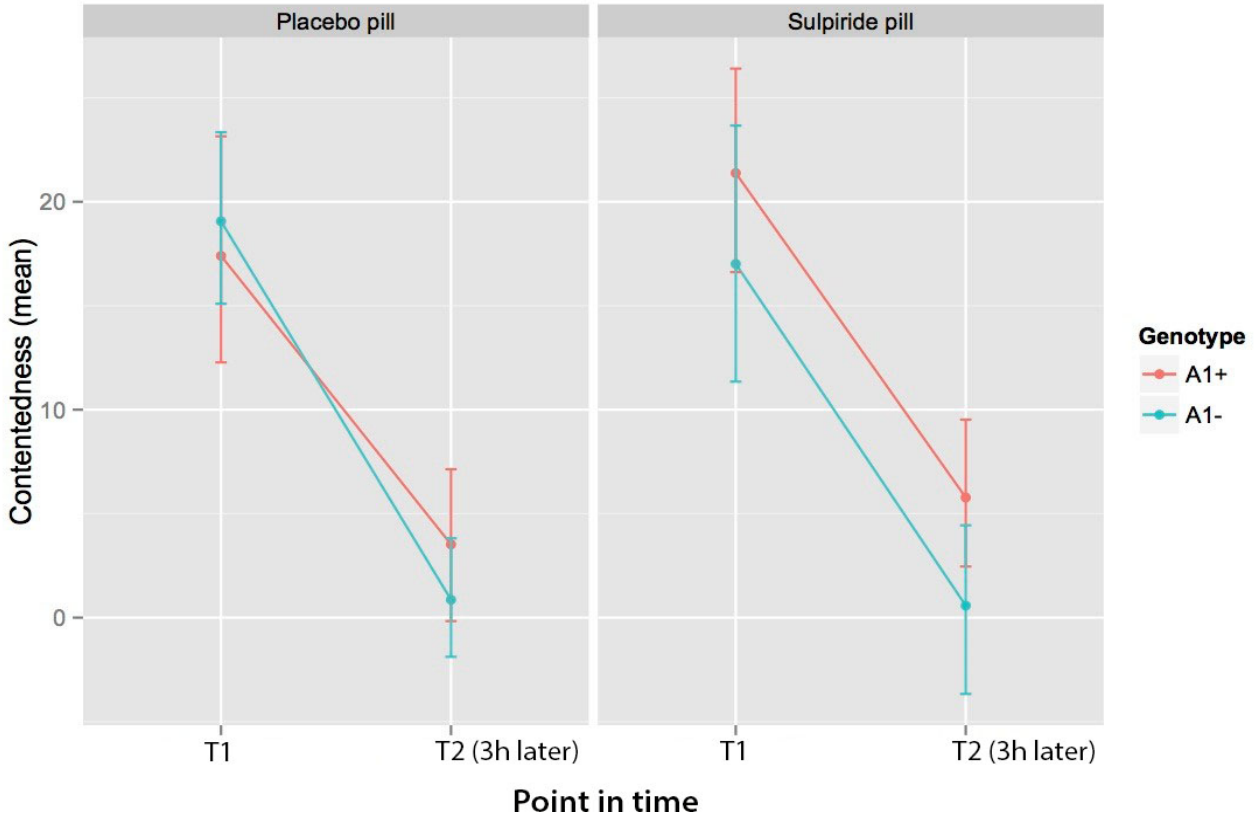
Figure 6 **A**ssessment of the alertness scale of the VAS at the baseline (T1) and second measurement, three hours after capsule ingestion (T2). Means are plotted ± error bars of 2SD.



Concerning the contentedness score, we also found a main effect on time [$F(1,70) = 80.63$, $P < 0.000$]. Post-hoc tests revealed that the contentedness score was significantly lower at the second measurement ($P < 0.000$) (Figure 7). Concerning group there was neither a significant main effect [$F(1,70) = 0.362$, $P = 0.548$] nor significant interactions (Ps > 0.164) on contentedness. All other main effects and interactions were not significant.

Regarding the calmness score there was likewise no significant main effect [$F(1,70) = 0.001$, $P = 0.970$] or interaction (Ps > 0.627) of group or any other Factor.

Figure 7 Contentedness assessment (VAS) at the baseline (T1) and second (T2) measurement, three hours after capsule ingestion. Means are plotted ± error bars of 2 SD.



Impulsivity measures (UPPS-P, Whiteside & Lynam, 2001)

The five sub-scales of the UPPS-P: negative urgency, lack of premeditation, lack of perseverance, sensation seeking and positive urgency were added to a general impulsivity score (Whiteside & Lynam, 2001).There was neither a correlation between the general impulsivity score and latency on the OTSOC (r = -.052) nor between impulsivity and accuracy of the OTSOC (r = -.03). We calculated a mixed ANOVA adding impulsivity (high versus low) as an additional between-subject factor.

Concerning latency at the OTSOC, there was a main effect of task difficulty [F(5,320) = 394.6, P < 0.000]. Further, there was a significant interaction between task difficulty and group [F(5,320) = 3.071, P = 0.023] and a significant four-way interaction between all included factors (group, genotype, task difficulty, impulsivity) [F(5,320) = 2.62, P = 0.044] (Figure 8). There was no significant main effect of impulsivity on latency [F(1,64) = 0.259, P = 0.612].

In question of accuracy in the OTSOC, there was a main effect of task difficulty [F(5,320) = 40.6, P < 0.000] and a significant main effect of group [F(1,64) = 7.22, P = 0.009] (Figure 8).

There were no significant main effect [$F(1,64) = 0.249$, $P = 0.619$] of impulsivity on accuracy but we found a trend for an interaction between genotype and impulsivity [$F(1,64) = 3.812$, $P = 0.055$]

Figure 8 Means of latency at the OTSOC including impulsivity as an additional between-subject factor. Means are plotted ± error bars of 2 SD.

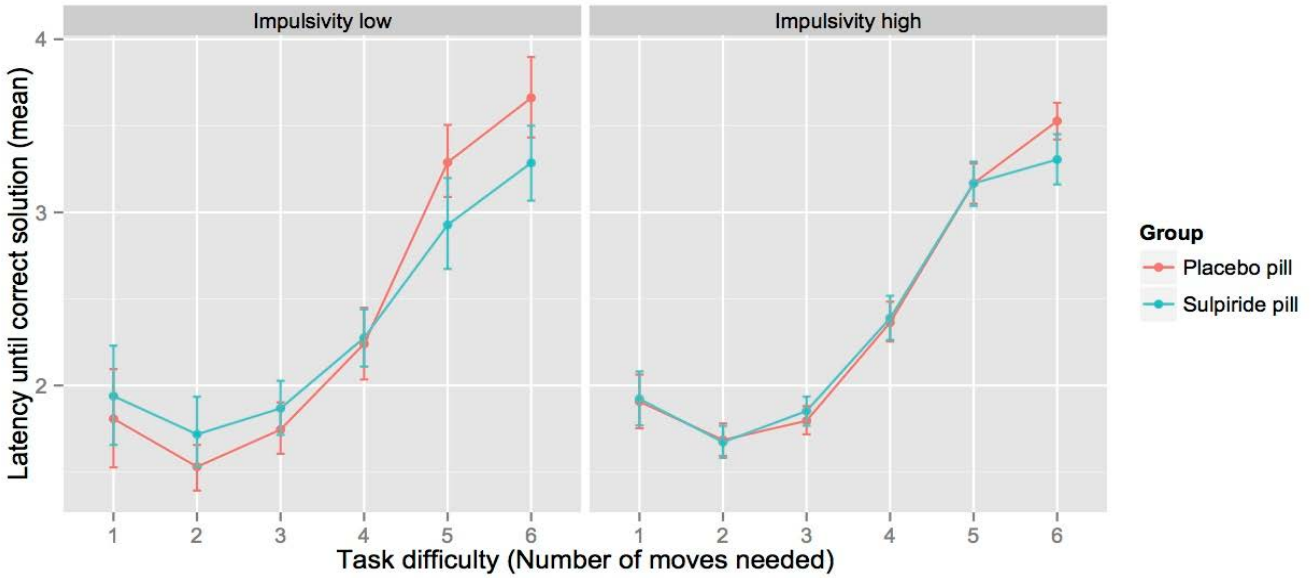
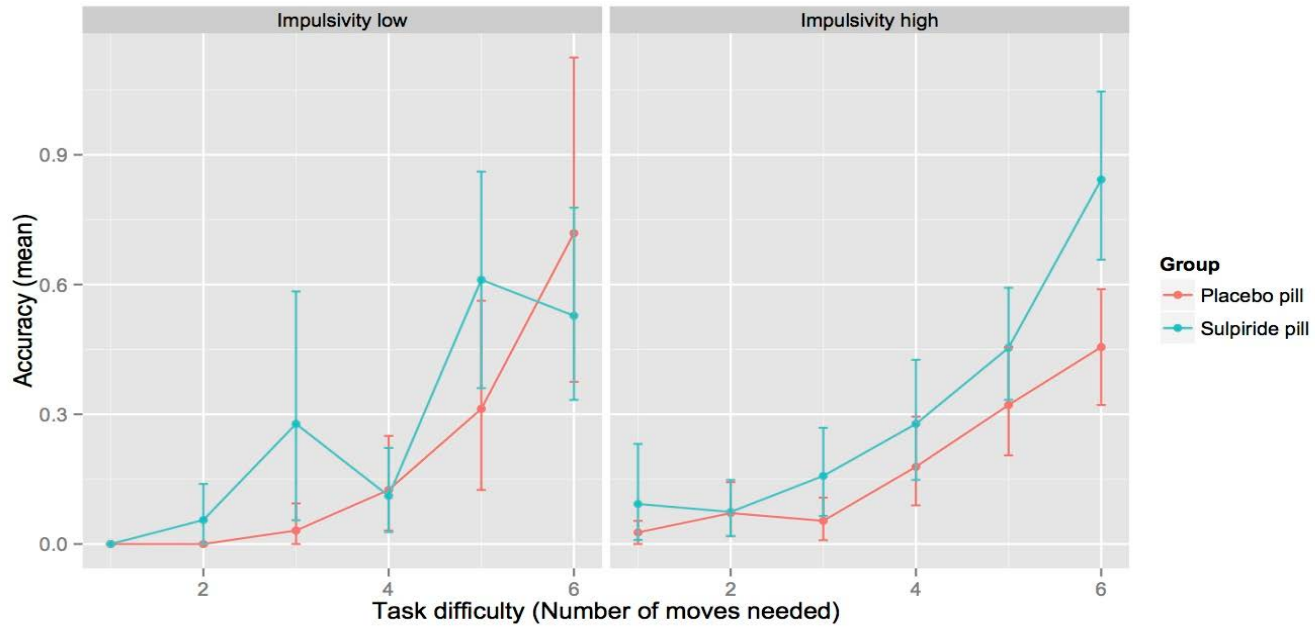


Figure 9 Means of accuracy at the OTSOC including impulsivity as an additional between-subject factor. Means are plotted ± error bars of 2 SD.



Discussion

This study investigated the effect of 800 mg of the dopamine D2/D3 antagonist sulpiride on planning performances at the OTSOC in healthy volunteers. Consistent with our hypothesis subjects administered with sulpiride were less accurate in solving the OTSOC compared with the placebo group. Concerning the time taken to correctly solve the task, we found that the sulpiride group was faster in solving the task at the more difficult levels of the OTSOC when including impulsivity as an additional between-subject factor in our model. In consideration of our second hypothesis we did not find greater impairment in subjects labelled with the A1+ allele that received the sulpiride pill. Regarding impulsivity, there was no correlation between impulsivity and latency in the OTSOC neither between impulsivity and the number of attempts made to solve the OTSOC.

As hypothesized, prolactin levels increased three hours after the ingestion of the pill only in the sulpiride group. Since high levels of prolactin are an indicator of post-synaptic dopamine receptor antagonism (Meites & Clemens, 1972; Turkington, 1972) this result can be interpreted as a manipulation check of post-synaptic dopamine receptor antagonism following sulpiride administration. In terms of our control variables blood pressure, pulse rate, alertness, calmness and contentedness, there were no differences between the sulpiride and the placebo group neither at baseline measurement nor three hours after capsule ingestion. This result indicates that our observed sulpiride effect is not attributable to be mediated by any of those control variables.

As expected, we found a difference in the number of attempts needed to solve the task, over the six task difficulty levels. The most difficult six-move problems needed significantly more attempts to be solved, compared with all other task difficulty levels. The same pattern of result was observed concerning the time taken to correctly solve the task. It is stated that simple planning (one-, two, or three-move problems) in the TOL tasks might be solved by simply using a visual matching-to-sample-strategy (Owen et al., 1997). Each ball has just to be moved directly to the position of the ball showed in the upper part of the display. Difficult planning in contrast (four-, five- or six-moves to solve the problem) requires to make visually counter-intuitive moves (Owen, 1997). In that case a ball has to be moved away from its final destination. Thus, it can be questioned if simple planning generally displays planning. According to that notion, simple planning problems in the OTSOC might be insensitive to the effects of sulpiride (Mehta, Sahakian, McKenna & Robbins, 1999). This would implicate that differences in planning performances between the two groups should be strongest at the more difficult problems. Although, we only found a trend for an interaction between task difficulty level and group, we did so in terms of latency, when including impulsivity as an additional factor in our model. This interaction indicated that the

sulpiride group was slower at the simple planning problems whereas they were faster in at the more difficult five- and six-move problems. Taking a closer look at the difference between high impulsive and low impulsive subjects (Figure 8) we can see that the presented interaction is very broad in the group of low impulsive whereas this is not the case in terms of high impulsive subjects. This pattern of result contrasts our hypothesis that the sulpiride group should be slower in solving the OTSOC compared with the placebo group. It is possible, that this contrasting result might be due to the difference between the original TOL task and its modified version (OTSOC) used in the present study. In the original TOL task subjects are required to physically encounter the sequences of moves needed to replicate the upper screen whereas this is not the case in the OTSOC. In terms of the original TOL task, latency displays the time taken to mentally generate the appropriate sequence needed before physically encountering this sequence. In the OTSOC, subjects are only required to select the number of moves needed from seven different boxes displayed on the screen without actually moving any of the balls. In a similar modified version of the TOL task used by Owen (1995) the time taken to correctly solve the task at the more difficult problems were almost twice as long compared to those observed in the original TOL task. Hence, shorter latencies in the original task might be due to the fact that subjects do not plan the required moves in total (as it is demanded) before starting to move the balls. On these grounds, solving the OTSOC requires much higher loads of working memory and thus might be more difficult to be solved in comparison with the original task. In the present study subjects that received the sulpiride pill might have had such troubles in solving the task at the more difficult levels, that they just guessed the correct answer without mentally generating the appropriate solution (planning). This supposition would explain our result, indicating that subjects administered with sulpiride were faster in solving the task at the more difficult levels but at the same time less accurate. Unfortunately, we are not able to detect if participants truly planned the sequence needed before initiating their response, in the present task setting. High impulsive subjects that received the placebo pill might have similarly guessed the correct solution without planning. This would explain the similar results of high impulsive subjects that received the sulpiride pill and those that received the placebo pill (see Figure 8). This similarity was not found with respect to low impulsive subjects.

Contradicting our second hypothesis, we did not find any performance differences between subjects labelled with the A1+ and subjects labelled with the A1- allele. The absence of this effect can be explained by the possibility that dopamine D2 receptors might not possess the proposed crucial role in planning. Since sulpiride is thought to have a similar affinity for D3 and D2 receptors (Caley & Weber, 1995; Möller, 2003), dopamine D3 receptors might play a more crucial role in planning than expected. To the others knowledge, there are no studies to date that investigated in the specific role

of dopamine D3 receptors in planning. Another possible explanation for the absence of an effect concerning striatal dopamine D2 receptor density, is based on the notion that dopamine D2/D3 receptors have also been found in mesolimbic areas as well as in the cerebral cortex (Murray, Ryoo, Gurevich & Joyce1994; Xiberas et al. 2001a; Möller, 2003). Thus, the absence of genetic effects could mirror greater functional blockade of cortical and limbic dopamine receptors, rather than striatal receptor occupation. This would be in line with a result by Xiberas et al. (2001b) indicating a preferential cortical versus striatal dopamine D2/D3 occupancy of amisulpride (similar to sulpiride).

In summary the present study replicated previous observations relating degeneration of the striatal dopamine system to planning difficulties (Lawrence et al., 1998; Owen et al., 1995; Sawamoto et al., 2008). As expected, our results contrast the result by Mehta et al. (2003) that indicated improved planning following sulpiride administration. As outlined above, their result might be due to predominant pre-synaptic receptor blockade following low doses (400 mg) of sulpiride. In the present study there was no functional consequence from pre-synaptic autoreceptor blockade exhibited, following high doses of sulpiride (800 mg). Hence, post-synaptic dopamine D2/D3 receptor blockade following sulpiride administration led to impaired planning in the present study.

Because successful planning is linked to the frontal cortex (Goel & Grafman, 1995; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Shallice, 1982) as well as the striatum (Lawrence et al., 1998b; Morris et al., 1988; Owen et al., 1995; Pavese et al., 2003), cognitive planning performance is assumed to be mediated by mechanisms within fronto-striatal circuitry (Alexander & Garett, 1986; Middleton & Strick, 1994). The concept of fronto-striatal circuitry suggests that both cortical and subcortical components are essential for efficient planning. Concerning the planning deficits exhibited in the present study, it is not clear if these display a disturbed striatal output. Given that we did not find an effect concerning striatal dopamine D2 receptor density it is possible that our effect resembles extrastriatal dopamine D2/D3 receptors blockade. Unfortunately, this issue cannot be answered within the present study. Further, it is important to keep in mind that for successful performance at the OTSOC a massive load on working memory is needed. Thus planning impairment at the OTSOC could also be a result of impaired working memory capacity (Dagher et al., 2001).

In conclusion, our results are in line with our hypothesis that dopamine D2/D3 receptors blockade results in impaired planning performance. To the authors knowledge, this is the first study to investigate the specific role of dopamine in planning in healthy volunteers administering high doses of sulpiride. If our observed sulpiride effect is predominantly linked to post-synaptic dopamine D2 receptor blockade or post-synaptic dopamine D3 receptor blockade can not be answered within the present study.

This issue could be investigated in future studies using a polymorphism linked to dopamine D3 receptor density. Furthermore, the question if the encountered sulpiride effect is due to predominant striatal or cortical post-synaptic receptor blockade remains unsolved and is likewise in need of further investigation.

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Curriculum Vitae

Persönliche Daten

Name:	Nele Motzki
Geburtstdatum:	26.04.1990
Staatsangeörigkeit:	Deutsch
E-Mail:	nelemotzki@gmail.com

Ausbildung

1996-2000:	Grundschule Klarenthal, DE
2000-2006:	Gesamtschule Sulzbachthal, DE
2006-2007:	Newport Highschool, USA
2007-2009:	Gesamtschule Sulzbachthal, DE Abschluss: Abitur
2010-2013:	Studium der Psychologie an der Universität Wien Abschluss: Bachelor of Science
2013:	Beginn des Master Studiums Psychologie an der Universität Wien
2013:	6-Wochenpraktikum bei der Social, Cognitive and Affective Neuroscience Unit (SCAN-Unit)