Motivational properties of reward associated stimuli

Conditioning studies with smoke and monetary reinforcement

Inaugural-Dissertation zur Erlangung der Doktorwürde der Philosophischen Fakultät II der Julius-Maximilians-Universität Würzburg

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Würzburg, 2014

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Tag des Kolloquiums: 23.07.2015

"Not every end is a goal. The end of a melody is not its goal: but nonetheless, had the melody not reached its end it would not have reached its goal either. A parable."

Friedrich W. Nietzsche, The Wanderer and His Shadow, § 204

„Nicht jedes Ende ist das Ziel. Das Ende der Melodie ist nicht deren Ziel; aber trotzdem: hat die Melodie ihr Ende nicht erreicht, so hat sie auch ihr Ziel nicht erreicht. Ein Gleichnis."

Friedrich W. Nietzsche, Der Wanderer und sein Schatten, § 204

Dedicated to my family

This thesis would have been hardly accomplished without the help and support of several persons. I cordially wish to thank …

Prof. Dr. Paul Pauli for offering me the opportunity to realize this work at his department. In particular, for his guidance, constructive comments, confidence and patience during the various stages of this project and - as I can really say - continuing support. I truly appreciate that.

Prof. Dr. Andreas Mühlberger for his scientific advice, (macro) support and collaborative trips into virtual environments.

Dr. Ronald F. Mucha for being a hoard of stimulating anecdotes and scientific knowledge. He shaped the development of this project from the *beginning*. Now, in the *end*, I can truly say that I benefitted from his critical way of thinking, his creativity and dedication to science. I learned a lot from him.

Prof. Dr. Matthias Wieser*, **Dr. Antje Gerdes***, **Dr. Marta Andreatta*** and **Dr. Annette Conzelmann*** for friendship, fun, mental and professional support - and for providing a wonderful acronym.

The various inhabitants of 007 who shaped - not only - the spirit of *my* office and made it a special place: **Dr. Hedwig Eisenbarth**, **Heike Ewald**, **Dr. Lingdan Wu**, **Dr. Youssef Shiban**, **Dr. Preeti Sareen**, **Dr. Philipp Reicherts***, **Hannah Genheimer*** and **Elena Flohr***.

* are particularly appreciated for shared proof reading

TABLE OF CONTENTS

ABSTRACT

Tobacco addiction is considered as a chronic relapsing disorder, characterized by compulsive drug seeking and intake. Learning processes are stressed to account for the situational-specific expression of core features of the disorder, e.g., craving for drug, tolerance and excessive consumption. According to incentive theories, smoke conditioned stimuli are hypothesized to be appetitive in nature, promoting craving, approach and consummatory behavior. Commonly, smoking cues are treated as simple excitatory conditioned stimuli formed by a close and reliable overlap with the drug effect. However, the smoking ritual comprises a multitude of stimuli which may give rise to different forms of learning and conditioned responses partially opposing each other. Previous research suggests the predictive content and the temporal proximity of smoking stimuli to the drug effect as important determinants of cue reactivity. In contrast to stimuli related to the preparatory stage of smoking and the start of consumption (BEGIN stimuli), stimuli from the terminal stage of smoking (END stimuli) apparently lack high cue reactivity. Several lines of evidence suggest the poor cue properties of terminal stimuli to be related to their signaling of poor smoke availability. Indeed, cue reactivity is commonly decreased when smoking appears to be unavailable. Moreover, the learning literature suggests that stimuli predictive for the non-availability of reward may acquire the capacity to modulate or oppose the responses of excitatory conditioned stimuli. Therefore, the aim of the present thesis was to enhance our knowledge of stimulus control in human drug addiction and incentive motivation by running a series of conditioning studies with smoke intake and monetary reward as reinforcer. Subjective report and physiological measures of motivational valence and consummatory response tendencies were used as dependent variables.

The *first experiment* of this thesis used a differential conditioning paradigm to reveal evidence for the conditioning of preparatory and consummatory responses to a CS+ for smoking. Neutral pictograms served as CSs and single puffs on a cigarette as US. In line with the predictions of incentive theories, the excitatory CS+ for smoking acquired the ability to evoke an appetitive conditioned response, as indicated by enhanced activity of the M. zygomaticus major. Moreover, anticipation of puffing on the cigarette increased the activity of the M. orbicularis oris (lip muscle), indicating the activation of consummatory response tendencies. Finally, the CS+ evoked stronger skin conductance responses, indicative of in-

creased autonomic arousal and orienting in preparation for action. In contrast, the rating data were apparently unaffected by the experimental contingency. In sum, the physiological data provide support for the notion that excitatory smoke conditioning gives rise to appetitive and consummatory conditioned responses, which may at least partially contribute to the maintenance of tobacco addiction.

The *second experiment* of this thesis adapted the conditioning protocol of the first study to probe the functional significance of terminal stimuli in the control of addictive behavior. This study manipulated the predictive relationship of BEGIN and END stimuli to smoke reinforcement to provide further support for the differential reactivity to both stimuli and the retarded (i.e., delayed) conditioning of END stimuli. Overall, the results of the first study of this thesis were conceptually replicated as the association of a BEGIN stimulus with smoke intake resulted in the acquisition of appetitive and consummatory physiological responses. Importantly, the results revealed evidence for a retarded excitatory conditioning of END stimuli. Thus, pairing of an END stimulus with smoke intake failed to produce a conditioned discrimination in terms of motivational valence and autonomic arousal, as indicated by the activity of the M. corrugator supercilii and the skin conductance data. These results provide further support for the notion that END stimuli may be weak cues for smoking. Moreover, in light of the results of the first study of this thesis, the retarded excitatory conditioning of terminal stimuli may be suggestive of an inhibitory response component, which may be related to their signaling of poor smoke availability. In sum, these results add to a growing body of data, which suggest that the expression of cue reactivity may be modulated by the temporal proximity and the availability of the drug effect.

The aim of the *third study* of this thesis was to provide "proof of concept" for an inhibitory conditioning notion of terminal stimuli. In this analog study BEGIN and END stimuli were emulated as discriminative S^D and S^Δ for monetary reward. During an acquisition phase conditioned inhibition was established to the S^Δ predictive of the non-availability of reward. Subsequently a retardation test was used to substantiate conditioned inhibition. In this test, excitatory conditioning of the previous S^Δ was compared to the excitatory conditioning of a novel control stimulus. Importantly, the results revealed evidence for reward conditioned inhibition as indicated by the retarded acquisition of subjective (pleasure and reward expectancy) and physiological (skin conductance and activity of the M. orbicularis oculi) responses. In sum, these results provide support for the notion that stimuli predictive

for the non-availability of reward may acquire the capacity to oppose the responses of excitatory conditioned stimuli. Thus, future research may benefit from the consideration of inhibitory conditioning processes in drug addiction, which may be of theoretical, methodological and clinical importance.

In sum, the present thesis revealed evidence for 1) an appetitive nature of excitatory conditioned smoking cues, 2) the dependency of this learning process on the temporal position of the conditioned stimuli in the intake ritual and 3) the acquisition of conditioned inhibition by a stimulus predictive for the non-availability of reward, as evident in retarded excitatory conditioning. Overall, these studies made a novel contribution to the field of human drug addiction and incentive motivation and provided valuable suggestions for further research.

ZUSAMMENFASSUNG

Tabakabhängigkeit wird als eine chronische Störung betrachtet, die durch exzessives drogensuchendes und -konsumierendes Verhalten gekennzeichnet ist. Lernprozesse werden zur Erklärung der Situationsspezifität zentraler Merkmale einer Abhängigkeit (z.B. Craving, Toleranz und übermäßiger Konsum) herangezogen. Anreiztheorien postulieren, dass konditionierte Rauchreize appetitiv sind, ein Verlangen zu konsumieren hervorrufen sowie Annäherungs- und konsummatorische Reaktionen induzieren. Gewöhnlich werden Rauch-Cues als einfache, exzitatorisch konditionierte Reize aufgefasst, die durch eine enge und reliable Überlappung mit der Drogenwirkung entstehen. Das Rauchritual beinhaltet allerdings eine Vielzahl von Reizen, die vermutlich unterschiedliche Lernformen begünstigen und dadurch teils einander entgegengesetzte konditionierte Reaktionen hervorrufen können. Die bisherige Forschung legt nahe, dass die zeitliche Nähe und der prädiktive Wert von Reizen hinsichtlich der Drogenwirkung die Cue-Reaktivität entscheidend beeinflussen. Im Gegensatz zu Reizen aus der präparatorischen Phase des Rauchrituals und solchen vom Konsumbeginn (Anfangsreize) lösen Reize aus der Endphase des Konsums (Endreize) nur geringe Cue-Reaktivität aus. Verschiedene Befunde legen nahe, dass die schwache Cue-Wirkung von Endreizen mit der wahrgenommenen Verfügbarkeit der Droge(nwirkung) zusammenhängt. So ist die Cue-Reaktivität gewöhnlich reduziert, wenn keine Möglichkeit zum Konsum besteht. Zudem legt die Lernliteratur nahe, dass Reize, die die Nicht-Verfügbarkeit einer Belohnung vorhersagen die Fähigkeit erwerben, exzitatorisch konditionierten Reaktionen entgegenzuwirken. Das Ziel der vorliegenden Arbeit war es somit, unser Verständnis der Reizabhängigkeit süchtigen Verhaltens und der zugrundeliegenden motivationalen Prozesse zu erweitern. Dazu wurde eine Reihe von Konditionierungsstudien mit Rauchaufnahme und Geldgewinn als Verstärker durchgeführt. Als abhängige Variablen wurde der Selbstbericht der Probanden sowie physiologische Maße motivationaler Valenz und konsummatorischer Reaktionstendenzen erfasst.

Im *ersten Experiment* dieser Arbeit wurde ein differentielles Konditionierungsparadigma verwendet, um den Nachweis zu erbringen, dass ein CS+ für Rauchen präparatorische und konsummatorische Reaktionen hervorruft. Dabei wurden neutrale Symbole als konditionierte Reize verwendet und einzelne Züge an einer Zigarette als US. In Übereinstimmung mit den Vorhersagen von Anreiztheorien löste der exzitatorische CS+ eine appetitive kondi-

tionierte Reaktion aus, die sich in einer erhöhten Aktivität des M. zygomaticus major zeigte. Zudem war die Aktivität des M. orbicularis oris (Lippenmuskel) erhöht, was für die Aktivierung konsummatorischer Reaktionstendenzen spricht. Schließlich rief der CS+ eine erhöhte Hautleitfähigkeitsreaktion hervor, die eine Orientierungsreaktion und erhöhte autonome Reaktivität im Rahmen der Handlungsvorbereitung anzeigt. Die experimentelle Kontingenz spiegelte sich jedoch nicht in den Reizbewertungen wieder. Insgesamt stützen die physiologischen Befunde die Auffassung, dass exzitatorisch konditionierte Rauchreize appetitive und konsummatorische Reaktionen auslösen, die zur Aufrechterhaltung einer Tabakabhängigkeit beitragen können.

Im *zweiten Experiment* wurde das Konditionierungsparadigma der ersten Studie adaptiert. Ziel des Experiments war es, die funktionellen Auswirkungen von Endreizen auf verschiedene Parameter abhängigen Verhaltens zu untersuchen. In der Studie wurde der prädiktive Gehalt von Anfangs- und Endreizen experimentell manipuliert, indem die Reize entweder als CS+ oder als CS- (und umgekehrt) mit Rauchen gepaart wurden. Zum einen sollten dadurch bisherige Befunde erweitert werden, die zeigen, dass beide Reize unterschiedliche Reaktionen auslösen. Zum anderen sollte der Nachweis einer verlangsamten exzitatorischen Konditionierung von Endreizen erbracht werden. Insgesamt konnten die Ergebnisse der ersten Studie der vorliegenden Arbeit konzeptuell repliziert werden. So lösten Anfangsreize appetitive und konsummatorische physiologische Reaktionen aus, wenn sie mit Rauchen gepaart wurden. Wichtiger jedoch war der Befund einer verlangsamten exzitatorischen Konditionierung von Endreizen, wie er sich in Maßen motivationaler Valenz (M. corrugator supercilii) und autonomer Erregung (Hautleitfähigkeitsreaktionen) zeigte. Diese Befunde stützen die Auffassung, dass Endreize nur eine schwache Cue-Wirkung besitzen. In der Zusammenschau mit den Befunden der ersten Studie sprechen die Ergebnisse andeutungsweise dafür, dass Endreize eine inhibitorische Reaktionskomponente besitzen. Diese könnte damit in Zusammenhang stehen, dass die wahrgenommene Verfügbarkeit der Droge(nwirkung) im Falle von Endreizen reduziert ist. Insgesamt gliedern sich die Befunde gut in eine Reihe von Studien ein, die nahelegen, dass Cue-Reaktivität durch die zeitliche Nähe und die Verfügbarkeit der Drogenwirkung moduliert wird.

Das Ziel der *dritten Studie* war es einen inhibitorischen Konditionierungsansatz zur Entstehung von Endreizen konzeptuell zu überprüfen. In einer Analogstudie wurden Anfangs- und Endreize als diskriminative Hinweisreize S^D bzw. S^Δ für einen Geldgewinn modelliert. In ei-

ner Akquisitionsphase wurde der S^{Δ}, der die Nicht-Verfügbarkeit eines Gewinns signalisierte, als konditionierter Hemmreiz etabliert. Anschließend wurde ein Retardationstest zum Nachweis konditionierter Hemmung durchgeführt. In diesem Test wurde die exzitatorische Konditionierung des ehemaligen S^{Δ} mit der exzitatorischen Konditionierung eines neuen Kontrollreizes verglichen. Dabei konnte konditionierte Hemmung in Form einer verlangsamten exzitatorischen Konditionierung subjektiver (positiver Affekt und Belohnungserwartung) und physiologischer (Hautleitfähigkeitsreaktionen und Aktivität des M. orbicularis oculi) Reaktionen nachgewiesen werden. Insgesamt stützen diese Befunde die Auffassung, dass Reize, die die Nicht-Verfügbarkeit einer Belohnung vorhersagen die Fähigkeit erwerben, exzitatorisch konditionierten Reaktionen entgegenzuwirken. Die weitere Suchtforschung könnte somit von einer stärkeren Berücksichtigung konditionierte Hemmprozesse sowohl hinsichtlich der Theorienbildung als auch in methodischer und klinischer Hinsicht profitieren.

Insgesamt hat die vorliegende Arbeit gezeigt, dass 1) exzitatorisch konditionierte Rauchreize eine appetitive Wirkung entfalten, 2) dieser Lernprozess von der zeitlichen Stellung der konditionierten Reize im Konsumritual abhängig ist und 3) Reize, die prädiktiv für die Nicht-Verfügbarkeit einer Belohnung sind als konditionierte Hemmreize fungieren können, was sich in einer verlangsamten exzitatorischen Konditionierung wiederspiegelt. Die vorliegende Arbeit erbrachte einen neuen Beitrag im Bereich der Sucht- und Motivationsforschung sowie mehrere Anknüpfungspunkte für zukünftige Forschungsvorhaben.

INTRODUCTION

From an evolutionary perspective organisms are confronted with the adaptive challenge to maximize reward and to minimize punishment (Darwin, 1859; Dawkins, 1976). Natural reward (e.g., food and water) can be considered as a multifaceted process, engaging neural systems mediating approach, consummatory behavior and learning (Barbano & Cador, 2007; Berridge & Robinson, 2003; Glickman & Schiff, 1967; Schultz, 2006). Commonly, reward experience is thought to affect future behavior based on the principles of associative learning. Accordingly, initially neutral stimuli, which become predictive of rewarding stimuli, can acquire control over physiological and behavioral responses directed to the desired outcome. From an incentive motivational perspective (see below: Motivational accounts of drug addiction) these stimuli are thought to elicit an appetitive central motive state, orchestrating the various response systems necessary for reward pursuit.

Although normally functional for survival, the powerful control of appetitive conditioned stimuli (CS) can become maladaptive, with negative consequences for the individual and the society. Drug addiction may be a prominent example of a psychopathological state, in which the processing of reward and reward predictive stimuli has gone astray. Besides alcohol, tobacco is probably the most commonly used drug in modern western societies. During the twentieth century tobacco consumption increased rapidly, presumably accelerated by the automation of cigarette production (Giovino, 2002). Cigarette smoking has been linked to various types of health problems, including cancer (e.g., Gandini et al., 2008; La Vecchia et al., 2010), cardiovascular (e.g., Ambrose & Barua, 2004; Teo et al., 2006) and pulmonary diseases (e.g., Rabe et al., 2007). Accordingly, it is considered as one of the major causes of preventable premature death (Doll, Peto, Boreham, & Sutherland, 2004; Peto et al., 1996; World Health Organization, 2013). Although the international effort on tobacco control has made substantial progress, worldwide an estimated billion of people smoke (World Health Organization, 2008).

A significant proportion of current smokers report an intention to quit (Mullins & Borland, 1996; Smit, Fidler, & West, 2011) which reached up to seventy percent in previous studies (Centers for Disease Control and Prevention, 2002). Furthermore, many smokers report at least one quit attempt during the last year (Centers for Disease Control and Prevention, 2002; West & Fidler, 2011; West, McEwen, Bolling, & Owen, 2001). However,

long-term abstinence seems to be difficult to accomplish, and rates have been reported as low as ten percent (Hatsukami, Stead, & Gupta, 2008; Hughes, Keely, & Naud, 2004; Moore et al., 2009), especially without further behavioral or pharmacological support (Eisenberg et al., 2008; Fiore et al., 2008; Hughes, 2009; Lancaster & Stead, 2005; Stead & Lancaster, 2005). Thus, smoking seems to be indeed an intractable habit to kick.

Previous research has established nicotine as the primary psychoactive component in tobacco that supports self-administration in animals and humans (Goldberg, Spealman, & Goldberg, 1981; Le Foll & Goldberg, 2006; Stolerman & Jarvis, 1995). Like many drugs of abuse, nicotine deploys its motivational impact at least partially by affecting brain mechanisms mediating natural reward and reward-related learning (Balfour, 2004; Di Chiara & Bassareo, 2007; Hyman, Malenka, & Nestler, 2006; Pierce & Kumaresan, 2006). Nicotine absorbed from cigarette smoke readily enters into the blood stream and binds to nicotinic acetylcholine receptors, a family of ligand-gated cation channels, in the peripheral and central nervous system (Benowitz, 2009; Brody et al., 2006; Changeux, 2010; Gotti et al., 2009). Central receptor binding is thought to initiate a cascade of neurotransmitter release in various neural and peripheral structures (Berrendero, Robledo, Trigo, Martin-Garcia, & Maldonado, 2010; Laviolette & van der Kooy, 2004; Watkins, Koob, & Markou, 2000). Although the neurobiological mechanisms underlying the reinforcement of nicotine self-administration are still poorly understood, several lines of evidence point to the importance of the mesocorticolimbic system (Balfour, 2004; Corrigall & Coen, 1991; Corrigall, Franklin, Coen, & Clarke, 1992; Di Chiara, 2000; Wonnacott, Sidhpura, & Balfour, 2005). This system was proposed to be crucially involved in mediating the addictive effects of a wide range of psychoactive drugs (Hyman et al., 2006; Koob & Le Moal, 2008; Panksepp, Knutson, & Burgdorf, 2002; Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984; Wise & Bozarth, 1987). While the precise functioning of this system is still a topic of cutting-edge research (Barbano & Cador, 2007; Berridge, 2007; Redish, 2004; Salamone, Correa, Farrar, & Mingote, 2007; Schultz, 2007; Wise, 2004), incentive notions of drug addiction emphasize its involvement in positive reinforcement and approach induced by drugs and drug-paired stimuli (Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987).

The repeated application of an addictive drug is hypothesized to give rise to multiple learning processes, which crucially contribute to the transition from recreational use to compulsive intake. Drug addiction is a complex disorder resulting from an interaction of

drug, genetic predispositions and environmental influences (Kalant, 2010; Spanagel, 2009). However, it seems clear that drug-related learning processes are especially important to account for the situational specific expression of core features of the disorder, e.g., compulsive drug seeking and intake, loss of control, tolerance, withdrawal and *craving*, i.e., a strong desire or urge for consumption. From its very beginning (Pavlov, 1927), animal research had a significant impact on the field of addiction and provided powerful protocols for translational research (Lerman et al., 2007; Markou et al., 1993; Sanchis-Segura & Spanagel, 2006). The drug conditioning literature indicates that through pairing with drug consumption previously neutral stimuli acquire the ability to elicit a plethora of conditioned responses. And indeed, there is rich evidence that this is the case for a multitude of response systems (Everitt & Wolf, 2002; Hyman et al., 2006; Kenny, Chen, Kitamura, Markou, & Koob, 2006; Le Foll & Goldberg, 2005; Self, 1998; Shaham, Shalev, Lu, de Wit, & Stewart, 2003; Siegel, Baptista, Kim, McDonald, & Weise Kelly, 2000; Stewart, 1992; Tzschentke, 2007; Weiss, 2010). This may include changes in physiological and motivational processes (Eikelboom & Stewart, 1982; Siegel et al., 2000; Stewart et al., 1984), attentional allocation (Robinson & Berridge, 1993) and overt drug seeking or drug taking behavior (Caggiula et al., 2001; Goldberg et al., 1981; Le Foll & Goldberg, 2005, 2006; Tzschentke, 2007). In its most simplified form each act of drug taking can be seen as a learning trial resulting in an association between environmental or internal stimuli and the effect of the drug on the organism. Accordingly, drug-associated stimuli (e.g., the sight, smell, taste, etc. of a cigarette for smokers) are hypothesized to evoke excitatory conditioned responses. The characteristic feature of drug *cues* is their ability to motivate self-administration of the drug and/or to elicit craving (see Drummond, 2001; Mucha, Pauli, Weber, & Winkler, 2008). The critical contribution of drug cues to the persistence of compulsive drug taking and its reinstatement after periods of extinction (Ciccocioppo, Martin-Fardon, & Weiss, 2004; Cohen, Perrault, Griebel, & Soubrie, 2005; Crombag, Bossert, Koya, & Shaham, 2008; LeSage, Burroughs, Dufek, Keyler, & Pentel, 2004; Shaham et al., 2003) is a well-documented phenomenon with important clinical implications. In the addicted human the presence of drug-associated stimuli is thought to promote further drug intake (Droungas, Ehrman, Childress, & O'Brien, 1995; Hogarth, Dickinson, & Duka, 2010; Mucha, Pauli, & Angrilli, 1998) and to prompt relapse in former drug users (Drummond, 2000; Grüsser et al., 2004; Heinz, Beck, Grüsser, Grace, & Wrase, 2009; Janes et al., 2010; Niaura et al., 1988; Shiffman, Paty, Gnys, Kassel, & Hickcox,

1996; Waters et al., 2004). Accordingly, it is essential to better understand the precise content of learning in drug-conditioning.

MOTIVATIONAL ACCOUNTS OF DRUG ADDICTION

A complete overview of theoretical accounts of drug-related learning processes is far beyond the scope of this thesis. The following paragraph selectively reviews influential models, basically derived from animal research, which emphasize the importance of aversive and appetitive motivational processes in drug-conditioned responding. As the conditioning studies of the present thesis were partially conducted under the framework of positive incentive theories, basic assumptions shared by these models are reviewed in more detail.

Early models of drug addiction emphasized the importance of negative reinforcement processes in the maintenance of compulsive drug taking. The repeated application of addictive drugs, like morphine, was demonstrated to result in the development of physical dependence. As drug discontinuation gives rise to unpleasant (physical or psychological) signs of withdrawal, further drug intake is reinforced negatively through the alleviation of discomfort. Abstinence induced withdrawal was assumed to motivate further drug intake through the alleviation of discomfort. Furthermore, withdrawal paired environmental stimuli were suggested to elicit conditioned withdrawal signs, including craving, which were addressed to account for relapse in former addicts (Ludwig & Wikler, 1974; Wikler, 1948).

Almost thirty years later Siegel (1975) revealed evidence for the importance of learning processes in the development of drug tolerance (i.e., a decrease in drug effect as a function of experience). Drug intake was seen as a challenge to homeostasis (i.e., the ambition of organisms to maintain a stable inner environment), which initiates unconditioned (physiological) responses with the adaptive function to counteract or compensate the pharmacological disturbance. Conditioned stimuli associated with drug intake were proposed to acquire the capacity to evoke these (conditioned) compensatory responses, thereby contributing to the maintenance of homeostasis (see also Poulos & Cappell, 1991; Ramsay & Woods, 1997). In the absence of drug these responses were suggested to manifest themselves as conditioned withdrawal signs and craving, thereby contributing to continued drug intake or relapse (Siegel et al., 2000).

Solomon and Corbit (1973, 1974) proposed a partially related model with a stronger focus on the temporal dynamics of affect (see also Schull, 1979). Addictive drugs were hypothesized to evoke a rapid positive affective state. This primary reaction (the *a* process) was proposed to be counteracted by a more sluggish and opponent reaction (the *b* process), which was hypothesized to underlie the emergence of aversive withdrawal signs and craving after cessation of drug intake. Conditioned stimuli directly preceding the onset of the *a* process (e.g., signals for the drug) were hypothesized to evoke both processes. In contrast, conditioned stimuli following the termination of the *a* process (e.g., signals for the absence of drug) were assumed to elicit the aversive *b* process only. Accordingly, they were suggested to act as negative secondary reinforcers, which motivate drug intake through relief of withdrawal and craving (see also Koob & Le Moal, 2008).

Positive incentive theories were introduced to overcome several limitations of traditional views of drug addiction. Stewart, de Wit, and Eikelboom (1984) argued that physical dependence is not necessary for the initiation or maintenance of self-administration of opiates or stimulant drugs (see also Wise & Bozarth, 1987). According to incentive theories, drugs directly act on neural systems mediating incentive functions of natural rewarding stimuli (primary incentives). Natural rewards are hypothesized to interact with the current state of the organism to generate an appetitive "central motive state" (Bindra, 1974; see also Toates, 1994). This positive affective state is thought to promote reward-directed actions dependent on the spatio-temporal arrangement of the environmental incentive stimuli. Accordingly, incentive stimuli excite a tendency to approach and contact the object, thereby eliciting consummatory behavior. Reward predictive stimuli are expected to acquire the ability to excite this central state, thereby triggering appetitive motivation attracting the organism towards them. Thus, dependent on their physical and temporal characteristics they come to evoke appetitive responses, which are assumed to reflect the general affective quality of the motivational state. Sometimes reward associated stimuli even elicit consummatory behavior or responses resembling the consummatory act (see also Craig, 1918; Dickinson & Dearing, 1979; Fanselow, 1994; Konorski, 1967; Sherrington, 1906; Timberlake, 2001, for differentiated discussions of the preparatory (appetitive) and consummatory stage of incentive processing, the interaction between different motivational systems and the importance of learning in the organization of motivational processes). Applied to the domain of drug addiction it was hypothesized previously that the activation of an appetitive

central state by drugs transforms stimuli paired with drug intake into powerful conditioned incentives. Thereby, they come to elicit a drug-like, "proponent" response (Stewart & Wise, 1992, p. 80), which motivates further drug seeking and consumption (Stewart, 1992; Stewart et al., 1984).

Robinson and Berridge (1993) basically followed Stewart et al. (1984) in their critic of negative reinforcement accounts of drug addiction, but disregarded the role of drug induced or conditioned pleasure. Instead, they hypothesized the ability to sensitize dopaminergic transmission in mesocorticolimbic systems as critical feature of addictive drugs. On a behavioral level sensitization is expressed as increased - psychomotoric - responding to repeated applications of a drug (behavioral sensitization). Partially based on evidence that affective facial expressions in taste reactivity studies were apparently unaffected by dopaminergic manipulations, Robinson and Berridge (1993) hypothesized that the mediation of the hedonic, pleasurable effects of drugs ("liking") is not the critical function of this system. Instead, they proposed the dopaminergic mesocorticolimbic transmission as necessary for the motivational process of incentive salience attribution (i.e., "wanting"). Accordingly, it is the attribution of heightened incentive salience to the "act of drug taking and to stimuli associated with drug taking" (p.266), which transforms them into salient, attractive and "wanted" incentives. Thus, the motivational impact of drug-paired stimuli does not necessarily reflect their hedonic properties. Furthermore, Berridge and Robinson (2003) proposed that in humans the hedonic quality of a motivational stimulus can be expressed as conscious subjective pleasure (liking, without quotation marks) or as core hedonic impact ("liking", with quotation marks) in form of objective affective reactions (e.g., facial expressions). Both psychological components of incentives do not necessarily have to coincide. A similar dissociation was hypothesized for the wanting component (wanting, without quotation marks). Thus, drug reward can comprise cognitive goals and explicit ratings of desire (i.e., craving for or wanting of drugs), which can be dissociated from objective measures of "wanting" (with quotation marks). Thus, drug cues can function as what was colorfully termed "CS motivational magnets" (Berridge & Winkielman, 2003, p. 508), thereby evoking conditioned approach (a "sign-tracking" response, i.e., approach of a CS predictive of positive - or negative - reinforcement). Moreover, cue evoked "wanting" can be seen as enhanced instrumental responding in Pavlovian-instrumental transfer tests (PIT). These tests measure the effects of separately trained CSs on instrumental responding, thereby controlling for simple S-

R reinforcement. These objective measures of "wanting" can be dissociated from sensitive indicators of "liking", e.g., affective facial expressions (Berridge & Kringelbach, 2008; Berridge & Winkielman, 2003). Thus, subjective wanting does not necessarily have to be experienced as pleasant in nature (liking), nor does it have to be accompanied by objective positive affective responses ("liking"). Conversely, positive affective responses ("liking"; e.g., positive facial expressions) do not necessarily have to be accompanied by conscious awareness of pleasure and can even be present despite subjective reports to the contrary.

To summarize, positive incentive accounts of drug addiction emphasize the ability of drug cues to evoke an appetitive motivational state. Dependent on theoretical perspective this may have several connotations in addition to mere signs of positive affect. However, important for the current work is the hypothesis that drug-paired stimuli acquire positive affective properties. In addicted humans, these responses may be revealed by objective and subjective measures of motivational valence, which can be dissociated from each other. The following paragraphs shortly review empirical support for this assumption derived from animal and human research.

APPETITIVE EFFECTS OF DRUG CUES IN THE ANIMAL LITERATURE

Most of the time the animal literature on drug-conditioning is far away from considering conditioned responses as a "fresh construction" (Bindra, 1974, p. 199) created by the interaction of organismic state and the distribution of incentive stimuli in the environment. However, there is considerable evidence for positive incentive properties of drug-associated stimuli as extensively reviewed elsewhere (Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987). In brief, the line of argumentation goes like this: drugs promote neurotransmitter (dopamine) release in the mesocorticolimbic system, which is also involved in the mediation of approach responses to natural incentives (see also Alcaro, Huber, & Panksepp, 2007; Barbano & Cador, 2007; Ikemoto & Panksepp, 1999; Nader, Bechara, & van der Kooy, 1997; Salamone, Correa, Mingote, & Weber, 2005; Schultz, 2007; Wise, 2004, for related and alternative hypotheses on dopaminergic functioning). Furthermore, addictive drugs are able to decrease the threshold of rewarding intracranial self-stimulation (Kenny, Koob, & Markou, 2003; Kenny & Markou, 2006; Markou & Koob, 1992; Wise, 1996), which is known to be capable to evoke approach and consummatory behavior (Glickman & Schiff, 1967; Olds, 1958; Trowill, Panksepp, & Gandelman, 1969). Animals – even nondependent

ones – self-administer various addictive agents (Stewart et al., 1984). By virtue of their association with the drug effect previously neutral stimuli may acquire the ability to activate mesocorticolimbic transmitter release (e.g., Ito, Dalley, Robbins, & Everitt, 2002; Vanderschuren & Kalivas, 2000; Weiss et al., 2000) and to decrease the threshold of intracranial self-stimulation (Hayes & Gardner, 2004; Kenny et al., 2003). Furthermore, drug cues may evoke behavioral approach (Bardo & Bevins, 2000; Tzschentke, 2007), promote the self-administration of drugs (Panlilio, Weiss, & Schindler, 2000; Weiss, 2010) and act as conditioned reinforcers (Di Ciano & Everitt, 2004; Everitt & Robbins, 2000). Finally, more sophisticated test-paradigms, such as Pavlovian-instrumental transfer tests, may provide further support for the motivational impact of drug stimuli on instrumental performance (Corbit & Janak, 2007; Glasner, Overmier, & Balleine, 2005, but see also Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009).

Although differences between several drugs of abuse have to be considered, nicotine seems to share several physiological and behavioral effects with other putative addictive agents (Le Foll & Goldberg, 2005, 2006; US Department of Health and Human Services, 1988; Wonnacott et al., 2005). Since previous demonstrations that nicotine can maintain drug seeking at high rates (Goldberg et al., 1981), substantial evidence has accumulated for its reinforcing effects (Corrigall, 1999). Furthermore, nicotine-conditioned stimuli can function as conditioned reinforcers and are thought to contribute essentially to nicotine self-administration (Caggiula et al., 2001; Cohen et al., 2005; LeSage et al., 2004; Palmatier et al., 2008). Moreover, nicotine can induce enhanced locomotor activity (Bevins & Palmatier, 2003; Shoaib, Schindler, Goldberg, & Pauly, 1997) and overt behavioral preference of environments associated with its application (Le Foll & Goldberg, 2005). Finally, nicotine administration was shown to reduce the threshold of intracranial self-stimulation (Harrison, Gasparini, & Markou, 2002; Kenny & Markou, 2006) and was demonstrated to stimulate neural transmission in mesocorticolimbic areas (Di Chiara, 2000; Wonnacott et al., 2005).

In sum, this short synopsis of basic animal research supports the role of positive incentive processes induced by the application of drugs and drug-paired stimuli in the control of addictive behavior. Yet, certainly this focused review does not deny the involvement of aversive motivational states (the "dark side of addiction" Koob & Le Moal, 2005), other conditioning (Everitt & Robbins, 2005; Koob & Le Moal, 2005; Siegel et al., 2000) and higher order cognitive processes (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Baler & Volkow,

2006; Bechara, 2005; Berridge & Robinson, 2003; Tiffany, 1990) in drug addiction. Instead, incentive-motivational theories may be seen as an elaborated and empirically grounded framework with integrative power (Hutcheson, Everitt, Robbins, & Dickinson, 2001). Thus, they can make an important contribution to our understanding of stimulus control in addictive behaviors.

APPETITIVE EFFECTS OF SMOKING CUES IN THE HUMAN LITERATURE

These observations from animal research accord with human studies, demonstrating that in drug users cue exposure can lead to prominent changes in subjective, physiological and behavioral responses (Carter & Tiffany, 1999; Hogarth et al., 2010; Hogarth & Duka, 2006; Niaura et al., 1988). In contrast to the animal literature, human research on the motivational properties of drug stimuli is mainly conducted by presenting participants naturalistic drug-associated cues, e.g., smoking paraphernalia (Carter & Tiffany, 1999). In these studies, drug stimuli from the intake ritual (e.g., the sight, smell, taste etc. of a cigarette) are often treated as simple excitatory conditioned stimuli, presumably established by their reliable association with the drug effect. Probably, the most extensively studied variable in cue reactivity research is self-reported craving to smoke. Accordingly, there is considerable evidence that smoking cues can evoke subjective craving (Carter & Tiffany, 1999), which might be further modulated by drug availability (Bailey, Goedeker, & Tiffany, 2010; Carter & Tiffany, 2001; Wertz & Sayette, 2001). Subjective pleasure as a reflection of an appetitive conditioned response is less commonly assessed. However, in line with classic incentive notions there are several reports that smoking cues can indeed evoke subjective liking (Carter & Tiffany, 2001; Mucha et al., 2008; Stippekohl et al., 2010). Interestingly, there is also evidence of nicotine-induced subjective pleasure in smokers. However, this effect is not always seen and often accompanied by concurrent reports of negative affect and confounded by conditions of deprivation and previous experience with the drug (Kalman, 2002; Kalman & Smith, 2005). Overall, the pleasurable potential of smoking as derived from self-report is probably less pronounced than in case of other drugs of abuse (Robinson & Pritchard, 1992).

While verbal report can indeed be valuable for clarifying the motivational processes underlying drug abuse in humans, the exclusive reliance on subjective data provides an incomplete basis of scientific theorizing. First of all, many psychological processes are not readily accessible to conscious insight, even in not addicted humans (Bargh & Chartrand,

1999; Nisbett & Wilson, 1977; Strack & Deutsch, 2004; Winkielman & Berridge, 2004). Thus, drug reward can be seen as multifaceted process involving different responses not necessarily reflected in conscious awareness (Berridge & Robinson, 2003). Several studies demonstrated that human drug users show a behavioral preference to self-administer low doses of a drug, which they were unable to discriminate from placebo on a subjective level (Hart, Ward, Haney, Foltin, & Fischman, 2001; Lamb et al., 1991). Furthermore, there is evidence that backward-masked drug and natural appetitive stimuli can evoke activation in mesocorticolimbic systems without accompanying conscious awareness (Childress et al., 2008). Moreover, even cue-evoked aversive subjective affect can be dissociated from physiological measures of appetitive motivation under certain circumstances (Grüsser et al., 2002; Mucha, Geier, Stuhlinger, & Mundle, 2000; Nees, Diener, Smolka, & Flor, 2012). In some cases this dissociation may reflect social demand effects, as drug addicted individuals may not always honestly report their subjective experience. This may be an attempt to downplay the total dimension of the disorder, or it may be motivated by guilt or legal issues (Goldstein et al., 2009). However, dysfunctions of neuronal circuits subserving interoception and self-awareness also have to be considered as an antecedent or a consequence of the disorder. Accordingly, objective measures of motivation are necessary to advance our understanding of stimulus control in addictive behaviors (Goldstein et al., 2009; Moeller et al., 2010).

CUE REACTIVITY STUDIES WITH NATURALISTIC SMOKING STIMULI

Cue reactivity research has developed a rich repertoire of research methods to study the impact of drug cues on current smokers. Traditionally, physiological measures have been applied to investigate whether cue-evoked responses mimic or oppose the effect of the drug. Most commonly, changes in heart-rate (HR) and skin-conductance were measured, with skin conductance responses (SCR) yielding higher effect sizes (Carter & Tiffany, 1999). Although the response pattern found does not seem to be drug-specific, it is at least suggestive for drug cues being of motivational relevance for smokers. This conclusion is further supported by studies showing that smoking cues capture the attention of smokers (as measured by a dot-probe task and/or eye tracking; see, for example, Field, Mogg, & Bradley, 2004; Mogg, Bradley, Field, & De Houwer, 2003). Furthermore, cue-evoked electroencephalographic (EEG) activity, e.g., an enhanced late positive potential (Versace et al., 2011) or a decreased startle-evoked P3 component (Versace et al., 2010), may index heightened "mo-

tivated attention" to smoking cues (Schupp et al., 2004). Interestingly, Mogg et al. (2003) found the attentional bias evoked by smoking cues (initial fixation) to be associated with higher pleasantness and craving ratings and a stronger symbolic cue-directed approach response (see also Bradley, Field, Mogg, & Houwer, 2004). This directly raises the question whether it is possible to test the motivational significance of smoking cues with physiological measures of motivational valence. If so, these may be fruitfully applied to advance our understanding of the emotional-motivational quality of cue-evoked responses and their relationship to phenomenological experience in humans.

So far human research on cue reactivity is based on at least two physiological indices of motivational valence. Previous animal and human research showed that the magnitude of the acoustic *startle response* increases linearly with the unpleasantness of an emotional state (Fendt & Mucha, 2001; Lang, Bradley, & Cuthbert, 1990). Geier, Mucha, and Pauli (2000) were probably the first who demonstrated that in smokers the startle response is inhibited during presentations of pictures of smoking cues. These appetitive effects of smoking cues were confirmed by later studies (Mucha et al., 2008) and other research groups (Cinciripini et al., 2006; Dempsey, Cohen, Hobson, & Randall, 2007; Muñoz, Idrissi, Sánchez-Barrera, Fernández, & Vila, 2011). Yet, this response pattern may be affected by deprivation from smoking (Cinciripini et al., 2006; but see Geier et al., 2000), individual differences (Dempsey et al., 2007; Muñoz et al., 2011; Orain-Pelissolo, Grillon, Perez Diaz, & Jouvent, 2004) and methodological factors (Elash, Tiffany, & Vrana, 1995; Mucha, Pauli, & Weyers, 2006).

Besides the affect-modulation of the startle response, the measurement of *facial muscular activity* has been proven to be a useful research tool in comparative affective neuroscience (Berridge & Robinson, 2003). Facial electromyography (EMG) can be used to capture subtle responses of several facial muscles which may be interpreted as an index of motivational valence (e.g., Lang et al. 1993). Most commonly researchers are interested in recording activity over the M. zygomaticus major ("smiling muscle") and the M. corrugator supercilii ("frowning muscle"). For example, Drobes and Tiffany (1997) used facial EMG to measure the activity of the zygomatic and corrugator muscle of smokers during exposure to smoking cues. This study reported that cue exposure enhanced the activity of the zygomatic muscle – indicative of increased positive affect - and reduced the activity of the corrugator muscle – indicative of decreased negative affect. In the study of Geier et al. (2000) smoking

cues, positive and neutral pictures evoked similar activity over the corrugator muscle, but less activity than negative pictures. Overall, these results are rather consistent with the predictions of positive incentive theories proposing an appetitive reaction to smoking cues. However, there are also contrary reports of cue-induced ambivalence (Griffin & Sayette, 2008). Thus, further research is needed to elucidate the situational specific expression of the motivational properties of smoking stimuli.

Besides their supposed appetitive impact, smoking cues are thought to promote further smoke intake. Accordingly, several studies examined the effect of smoking cues on various components of the topography of smoking. For example, there is evidence that cue exposure decreases the latency to initiate smoking (Droungas et al., 1995; Payne, Schare, Levis, & Colletti, 1991; Surawy, Stepney, & Cox, 1985), enhances the number of puffs on a cigarette (Hogarth et al., 2010; Surawy et al., 1985) and increases the duration of smoking (Payne et al., 1991; but see also Shiffman et al., 2013a; Shiffman et al., 2013b). However, this effect can be interpreted from different theoretical perspectives (focusing on habit-learning, specific drug-goal-expectancies or conditioned emotional states), which cannot be fully evaluated without further tests (e.g., Pavlovian-instrumental transfer tests; see, for example, Hogarth et al., 2010). Yet, the important implication of these studies is that smoking cues may evoke a tendency to engage in the consummatory act. Thus, one can hypothesize that motor activity in anticipation of the consummatory response can actually become conditioned to smoke-paired stimuli.

CONDITIONING STUDIES WITH SMOKE INTAKE AS REINFORCER

Overall, the results of the studies reported above provide at least partial evidence for the involvement of appetitive motivational mechanisms in cue-evoked responding, which may eventually give rise to consummatory behavior. Although cue reactivity research is valuable for our understanding of stimulus control in addictive behaviors, it necessarily has to be silent about whether this reactivity is indeed the result of conditioning (Robbins & Ehrman, 1992). Experimental evidence for this learning process comes from studies which actually paired previously neutral stimuli with smoke reward in the lab. In human research the learning process underlying tobacco-dependence is often emulated by associating artificial stimuli with an opportunity to smoke. Although there are some reports of conditioned subjective pleasure, evidence from physiological measures of motivational valence is lacking (see be-

low). This is further surprising given the clear importance of this empirical question for current theorizing (Robinson & Berridge, 1993; Stewart et al., 1984). An early study conducted by Lazev, Herzog, and Brandon (1999) used a differential conditioning paradigm with smoking of a single cigarette as unconditioned stimulus (US). This study showed that compared to the CS- (i.e., the unpaired CS) the smoking associated CS+ (i.e., the paired CS) increased craving, positive affect and pulse rate. Mucha et al. (1998) demonstrated that smokers preferred listening to an auditory CS+ previously associated with smoking. Importantly, compared to the CS- the participants also spent more time drawing on a cigarette during the presentation of the CS+. Furthermore, when the CS+ was presented later under conditions of extinction activity of the trapezius muscle (involved in the motor act of smoking) was enhanced during the time slot smoking was available previously. Taken together, these results suggest that through pairing with smoke consumption previously neutral stimuli may acquire the ability to promote or maintain smoke intake behavior even under conditions of extinctions. Finally, Field and Duka (2001) measured cue-evoked salivation as possible index of an appetitive motivational state evoked by a smoke paired CS+. Although the CS+ increased subjective craving, the results were inconsistent regarding to CS+ evoked salivation.

All studies reported above used the smoking of an entire cigarette as unconditioned stimulus. However, even single puffs on a cigarette may be sufficient to support learning. For example, Lewin, Biglan, and Inman (1986) showed that single puffs can be used to reinforce increases in the activity of the frontalis muscle (located at the front of the head). Furthermore, Carter and Tiffany (2001) demonstrated in an influential study that the availability of single puffs on a cigarette enhanced cue-evoked craving and pleasure (see also Bailey et al., 2010). Moreover, skin conductance responses were increased and the response latencies to initiate smoking were decreased. Finally, Hogarth, Dickinson, and Duka (2003a) used a discriminative conditioning paradigm and showed that a S^D (i.e., a stimulus, which sets the occasion for an instrumental response leading to reinforcement; in contrast reinforcement is omitted in case of a S^Δ) for single puffs on a cigarette increased selective attention and skin conductance responses (see also Hogarth & Duka, 2006). Overall, these results support the notion that previously neutral stimuli paired with smoking become conditioned cues and evoke responses similar to naturalistic smoking cues. However, human conditioning studies with objective measures of motivational valence only delivered hints that smoking cues elicit appetitive reactions in smokers. Moreover, only a few studies were interested in

the conditioning of motor responses necessary for the consummatory act (Mucha et al., 1998).

To summarize, incentive theories propose smoking cues to be appetitive and to support consummatory intake behavior. Human research on cue reactivity provided partial evidence for this assumption stemming from subjective data and objective measures. In contrast to the vast amount of studies investigating naturalistic smoking stimuli, conditioning studies with smoke intake as US are scarce. Moreover, to the best of my knowledge there are no further studies which included more sensitive physiological measures of motivational valence. Furthermore, an important contribution to the human smoke conditioning literature could be made by demonstrating conditioned changes in motor activity in anticipation of puffing on a cigarette. Thus, considering the theoretical importance and available empirical data it seems imperative to provide support for the conditioning of preparatory physiological responses in human smokers, which was the aim of the *first experiment* of this thesis (see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers).

CORE FEATURES OF CONDITIONING

Furthermore, the predictive value of current theories may be enhanced by a more stringent focus on core features of learning. Thus, it may be important to consider the temporo-spatial relationship of conditioned stimuli to the unconditioned stimulus, their modulatory properties and predictive content, which are commonly addressed in the animal drug literature in less detail. Generally, temporal contiguity has been considered as a necessary determinant of learning (Wasserman & Miller, 1997). Surprisingly, the influence of temporal parameters on conditioning has been relatively neglected by prominent associative accounts (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972), although modern theories increasingly emphasize their importance (Arcediano & Miller, 2002; Brandon, Vogel, & Wagner, 2003; Savastano & Miller, 1998; Wagner & Brandon, 1989). Commonly, conditioned responding is hypothesized to decrease as the CS-US interval is increased. However, there is considerable evidence that manipulations of the temporo-spatial relationship do not simply have an effect on the strength of conditioned responding. Instead, the *form* of conditioned responses is affected by the temporo-spatial arrangement and physical characteristics of conditioned and unconditioned stimuli, which determines the interaction of an organism with various types of incentives (Bindra, 1974; Domjan, 2005; Fanselow, 1997; Timberlake, 2001). Thus, the conditioning of behavioral response tendencies, perceptual sensitivities and physiological regulatory changes may be differentially affected by the proximity of the incentive stimuli. Roughly, one may assume a short CS-US interval as less crucial for the acquisition of preparatory motivational responses. Thus, appetitive responses like approach can be even seen with "distal" CSs of long duration. In contrast, "proximal" CSs may be prone to acquire the ability to elicit consummatory responses (Dickinson & Dearing, 1979, p. 211; Konorski, 1967). Thus, the nature of the conditioned response may be dependent on the proximity of the US. For example, there is evidence from a sexual conditioning preparation in male Japanese quail (Akins, Domjan, & Gutierrez, 1994) that a relatively short CS-US interval (1 min) may support conditioning of an approach response (probably reflecting focal search behavior). In contrast a CS+ of long duration (20 min) was seen to primarily evoke pacing behavior (probably reflecting general search behavior). Moreover, the presentation of a CS formed by a short CS-US interval may support the conditioning of consummatory response tendencies, although overt consummatory behavior (e.g., copulation) may be only seen under special circumstances (e.g., for a CS comprising species-

specific stimulus features; see Akins, 2000). These results are partially mirrored by conditioning studies with rodents which used food reward as US and revealed evidence suggestive for the conditioning of general and focal search behavior to conditioned stimuli with long and short CS-US intervals, respectively (Silva & Timberlake, 1997; Timberlake, 2001).

Applied to the domain of drug conditioning the studies cited above suggest that drug stimuli can evoke different responses dependent on their temporo-spatial relationship to drug reward. And indeed, there is evidence that temporal factors may have a drastic influence on the outcome of drug conditioning and may even switch behavioral preference to overt aversion (Bevins, Eurek, & Besheer, 2005; Cunningham, Okorn, & Howard, 1997; Cunningham, Clemans, & Fidler, 2002; Cunningham, Gremel, & Groblewski, 2006; Fudala & Iwamoto, 1987; Fudala & Iwamoto, 1990; Schwarz-Stevens & Cunningham, 1993). However, such effects can be influenced by the dose of drug, route of administration and type of species. Yet, considering the functional relevance of drug conditioned responses one may hypothesize that the acquisition of preparatory responses might be less dependent on a close temporal contiguity with the drug effect than the conditioning of consummatory response tendencies (see above). Furthermore, the development of conditioned compensatory responses may require a closer overlap with the drug effect (Mucha, Geier, & Pauli, 1999). According to pharmacological theories the adaptive function of compensatory response conditioning is seen in the maintenance of homeostasis (Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel, 1975, 1989). Thus, stimuli most closely connected to the physiological disturbance and the elicitation of the unconditioned compensatory responses produced by the drug may be especially prone to this form of conditioning (see Eikelboom & Stewart, 1982; Poulos & Cappell, 1991; Ramsay & Woods, 1997, for elaborated discussions of the intricacy to correctly identify the (un)conditioned stimuli and (un)conditioned responses). At least, some conditioning studies with morphine in rodents suggest that a close temporal proximity between conditioned stimuli and the drug effect may be important for the acquisition of physiological (thermal and heart-rate) responses (Broadbent & Cunningham, 1996; Schwarz-Stevens & Cunningham, 1993). Overall, these arguments suggest that the reactivity evoked by drug stimuli may be influenced by their temporo-spatial relationship to the drug effect (see also Tindell, Berridge, Zhang, Peciña, & Aldridge, 2005). Moreover, manipulations of the temporal relationship between the CS and US may actually affect the experimental contingencies.

Besides temporal parameters associative learning is crucially driven by the predictive relationship between conditioned stimuli and the unconditioned stimulus. Thus, during conditioning previously neutral stimuli are hypothesized to acquire informational value regarding to the incidence and nature of the US (e.g., Kamin, 1968; Rescorla, 1968, 1988). Accordingly, excitatory conditioned stimuli can be seen as signals predictive for a *change* in the environment with motivational importance. They may provide information about the availability of reward, thereby enabling an organism to prepare for an upcoming incentive object and to deal appropriately with it (Hollis, 1997). If the association of a stimulus with an US endows it with the capacity to elicit excitatory responses, this directly raises the question whether the association of stimuli with the non-availability of an US might give rise to conditioning? This seems to be a simple question at first glance, as an association with nothing might condition nothing at all. Thus, in standard conditioning paradigms the non-rewarded control stimulus (CS- or S^{Δ}) might simply become inert or stay neutral. However, classic accounts of learning propose that signals for the non-availability of a reinforcer may acquire response tendencies opposite to those controlled by excitatory conditioned stimuli (Hearst, 1972; Konorski, 1967; Pavlov, 1927; Rescorla, 1969; Savastano, Cole, Barnet, & Miller, 1999). Sometimes the reactivity evoked by these conditioned inhibitors[1] may be easily expressed

[1] The terms *conditioned inhibition*, *inhibitory conditioning* or *inhibitory learning* are used in a broader context and subsume paradigms, commonly assumed to involve some form of inhibitory learning. In these paradigms the inhibitory trained stimulus is commonly labeled as X and the training excitor as A. Examples include Pavlovian (A+/AX-), differential (A+/X-) or discriminative (operant) conditioned inhibition (S^{D}/S^{Δ}), conditional discrimination (AB+/BX-), (serial) feature-negative conditioning/occasion, setting (A+/X->A-) and context dependent forms of inhibition. Although the later may provide a link into inhibitory processes involved in extinction *learning* (see, for example, Bouton, 2004; Crombag et al., 2008; Maren, Phan, & Liberzon, 2013), the corresponding literature is hardly touched. The same is true for studies on backward conditioning (e.g., Andreatta, Mühlberger, Yarali, Gerber, & Pauli, 2010; Silva, Timberlake, & Cevik, 1998; Spetch, Wilkie, & Pinel, 1981) and research with a broader link to the construct of inhibition (e.g., Bari & Robbins, 2013; Eagle, Bari, & Robbins, 2008). The term *conditioned inhibitor* commonly refers to stimuli with conditioned inhibitory properties (see the operational definition in: A primer on conditioned inhibition). Occasionally, the term is used more precisely to acknowledge differences (and sometimes commonalities) between several forms of inhibitory conditioned stimuli (most of the time when (serial) feature-negative conditioning/occasion setting is addressed (see, for example, Swartzentruber, 1995). In contrast to Pavlovian conditioned inhibition (A+/AX-), in (serial) feature-negative conditioning (A+/X->A-) the inhibitory conditioned feature X is presented before the training excitor A. This form of inhibition may mirror the one involved in context dependent extinction (i.e., a form of modulation).

in overt behavior. For example, in conditioning studies measuring the acquisition of a sign-tracking (approach) response in pigeons to a CS+ for food reward, a stimulus signaling the non-availability of food (CS-) was seen to evoke an avoidance response (Hearst, Bottjer, & Walker, 1980; Wasserman, Franklin, & Hearst, 1974). However, conditioned inhibition may not always be symmetrical and mutually exclusive to conditioned excitation (Baker, 1974; Droungas & LoLordo, 1994; Falls & Davis, 1997; Lysle & Fowler, 1985; Rescorla, 2005; Williams & Overmier, 1988; Zimmer-Hart & Rescorla, 1974). In contrast to excitatory stimuli, putative conditioned inhibitors or negative occasion setters (i.e., CSs with *modulatory* properties which decrease the responses to other conditioned stimuli through a process presumably not dependent on a direct inhibitory association with the US) often fail to evoke clearly observable responses (Holland, 1984; Holland & Coldwell, 1993; Rescorla, 1987; Swartzentruber, 1995). Instead, their effect may be dependent on the presence of an excitatory stimulus, which evokes reactivity they can modulate. Accordingly, there might be a measurement problem in the detection of inhibition (see below: A primer on conditioned inhibition), as for inhibition to be seen, some level of excitation has to be present. Thus, one may probe inhibitory processes by assessing the capability of a putative inhibitor to reduce the reactivity evoked by a concurrently presented excitatory stimulus (i.e., a summation test). Furthermore, a conditioned inhibitor should show a resistance to excitatory conditioning evident as delayed, i.e., retarded conditioning (hence the name retardation test; see Hearst, 1972; Konorski, 1948; Rescorla, 1969; Savastano et al., 1999 ; Williams, Overmier, & LoLordo, 1992). For example, a conditioned inhibitor of food was shown to decrease behavioral responding (head entries of rodents into a food cup) evoked by an excitatory CS (summation test). Conversely, the putative inhibitor only reluctantly acquired the ability to evoke head entry responses under conditions of food reinforcement – i.e., the CS passed a retardation test (Williams, Johns, & Brindas, 2008). Thus, stimuli paired with the non-availability of reward may actually acquire inhibitory properties (but see also Tinsley, Timberlake, Sitomer, & Widman, 2002, who argued from a behavior systems approach that the nature of the response may be dependent on the test situation), which was even demonstrated on a neuronal level (Matsumoto & Hikosaka, 2007; Tobler, Dickinson, & Schultz, 2003, but see also Matsumoto & Hikosaka, 2009) .

Despite their important role in basic research and theorizing, inhibitory conditioning processes are commonly neglected in the animal drug conditioning literature. As described

above this research strongly highlights the potency of drug cues as predictive signals for drug in the control of conditioned responding. Thus, drug-conditioned excitatory stimuli are assumed to evoke drug seeking and intake. Based on the classic learning literature one may hypothesize that stimuli signaling the non-availability of drug may acquire inhibitory response properties. Interestingly, there are several enlightening reports which suggest that core features of drug addiction, e.g., tolerance (Fanselow & German, 1982; Hinson & Siegel, 1986; Siegel, Hinson, & Krank, 1981; Vila & Miranda, 1994), sensitization (Stewart & Vezina, 1991; Vezina & Leyton, 2009) and even instrumental drug seeking behavior (Kearns, Weiss, Schindler, & Panlilio, 2005; Mihindou, Guillem, Navailles, Vouillac, & Ahmed, 2013; Weiss et al., 2007), can come under inhibitory stimulus control (see below: A primer on conditioned inhibition). Thus, the consideration of inhibitory learning processes in drug addiction has major theoretical, methodological and clinical implications.

POOR CUE EFFECTS OF TERMINAL SMOKING STIMULI

As reviewed above, human cue reactivity is often treated in the framework of a simple conditioning model. Thus, stimuli from the drug intake ritual are seen as conditioned stimuli formed by their close and reliable overlap with the drug effect. Although there is considerable evidence that not all drug stimuli are created equal (see Baker et al., 2004; Eikelboom & Stewart, 1982; Everitt & Robbins, 2005; Koob & Le Moal, 2008; Robinson & Berridge, 1993; Siegel, 1975; Solomon & Corbit, 1973; Stewart et al., 1984; Vezina & Leyton, 2009; Wikler, 1948, and: Motivational accounts of drug addiction) most commonly they are assumed to act as drug cues. Thus, they are hypothesized to evoke high craving and/or self-administration of drug. However, there is a conundrum in the literature as stimuli from the terminal stage of the smoking ritual (END stimuli) apparently fail to evoke the high reactivity seen for normal smoking cues (Mucha et al., 2008), i.e., stimuli prior to or from the start of consumption (BEGIN stimuli). This is rather surprising as terminal stimuli are clearly associated with smoking and seem to differ from cues only in minor aspects. Moreover, terminal stimuli are probably optimally placed in the smoking ritual to acquire conditioned responses. Nicotine, the pharmacological agent thought to give rise to conditioning, reaches peak levels in the blood probably about the time when a cigarette is finished (Benowitz, 1990; Jarvik et al., 2000; Mucha et al., 2008). Accordingly, terminal stimuli closely overlap with the drug effect which is one important determinant of conditioning. And even under less opti-

mal preconditions the huge number of pairings (i.e., smoked cigarettes) during a smoking career should give rise to conditioned responses finally mirroring those of cues (Mucha et al., 2008). However, a series of studies revealed considerable evidence that the CS properties of terminal stimuli diverge from those of normal cues.

BEHAVIORAL AND PSYCHOPHYSIOLOGICAL STUDIES ON TERMINAL STIMULI

Several experiments with picture stimuli from the smoke intake ritual used to model BEGIN and END stimuli consistently demonstrated that END stimuli do not evoke the high craving response seen for BEGIN stimuli. This was shown for different picture sets and stimuli closely matched for physical content (Bushnell et al., 2000; Mucha et al., 2008; Mucha et al.; Mucha et al., 2006; Stippekohl et al., 2010). Moreover, END stimuli were rated as more unpleasant than both BEGIN stimuli and neutral control material, respectively. Importantly, these differences were not seen in never-smokers (Mucha et al., 1999). Thus, END stimuli may evoke responses different from and maybe opposite to the hypothesized appetitive effects of smoking cues. Furthermore, END stimuli fail to evoke a strong appetitive response as indicated by an inhibition of affect-modulated startle (Mucha et al., 2008; Mucha et al., 2006; but see also Rehme et al., 2009). In contrast, previous research revealed considerable evidence for an appetitive nature of smoking cues (Cinciripini et al., 2006; Dempsey et al., 2007; Geier et al., 2000; Muñoz et al., 2011). Yet, this effect may be attenuated by a tendency not to engage in smoking, as induced by satiation (Cinciripini et al., 2006; but see Geier et al., 2000), motivation to quit smoking (Dempsey et al., 2007; Muñoz et al., 2011; Stippekohl et al., 2012b) or non-availability of drug (Bailey et al., 2010; Mucha et al., 2008). Moreover, END stimuli seem to lack high incentive "salience" which is considered as another critical feature of drug cues. Commonly, drug cues are hypothesized to capture attention and several studies revealed evidence for an attentional bias towards smoking cues in smokers (Field & Cox, 2008; Field et al., 2004; Hogarth et al., 2003a; Hogarth, Dickinson, & Duka, 2009; Mogg, Field, & Bradley, 2005; Waters et al., 2009a; Waters, Shiffman, Bradley, & Mogg, 2003). Enhanced attentive processing was further shown to be correlated with cue-evoked subjective craving (Hogarth et al., 2003a; Waters et al., 2009a), physiological responses (Hogarth et al., 2003a; Waters et al., 2009a) and symbolic approach behavior (Mogg et al., 2005). Concordantly, BEGIN stimuli were shown to elicit early attentional engagement (Stippekohl et al., 2012a). Although Stippekohl et al. (2012a) failed to

provide evidence for the specificity of this bias in nondeprived smokers, this study revealed a unique neuronal response pattern evoked by BEGIN stimuli (see below). In contrast, END stimuli failed to capture attention. Moreover, parts of the response data were even suggestive of attentional disengagement, although this hypothesis is in need for further validation. These findings provide further evidence for the weak cue properties of terminal smoking stimuli and may be especially interesting in light of the results of studies, which addressed the possible mechanisms underlying this effect (see below).

FUNCTIONAL NEUROIMAGING STUDIES ON TERMINAL STIMULI

Finally, a disparate neural response pattern of BEGIN and END stimuli was revealed using fMRI (Stippekohl et al., 2010). END stimuli were shown to evoke a distinct pattern of activations and even deactivations in structures of a broadly distributed "addiction network", including mesocorticolimbic circuits. This network was hypothesized as neural correlate of different components of drug reward (David et al., 2005; Due, Huettel, Hall, & Rubin, 2002; Franklin et al., 2007) and described previously as including circuits comprising the ventral tegmental area, ventral striatum, hippocampus, amygdala, insula, orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) (Engelmann et al., 2012; Everitt & Robbins, 2005; Naqvi & Bechara, 2009; Naqvi & Bechara, 2010; Volkow, Fowler, & Wang, 2003; Volkow, Fowler, & Wang, 2004; Wilson, Sayette, & Fiez, 2004). BEGIN stimuli lead to reliable activations in this network in smokers (e.g., in the ventral tegmental area, ventral striatum, insula and DLPFC). In contrast, END stimuli evoked a more differentiated pattern of activations and even deactivations (e.g., in parts of the ventral striatum and ACC). These structures have been suggested previously as important correlates of incentive motivation, reward anticipation, discrimination learning and conflict detection (Braver, Barch, Gray, Molfese, & Snyder, 2001; Kirsch et al., 2003; Knutson, Adams, Fong, & Hommer, 2001; Knutson & Cooper, 2005; Martin-Soelch, Linthicum, & Ernst, 2007; Robinson & Berridge, 1993). Thus, deactivations in these structures may be indicative of an attenuation of an incentive motivational state by END stimuli. Interestingly, previous studies using extracellular recordings of single dopaminergic neurons in monkeys found depressed activity in response to the unpredicted omission of a natural reward (Schultz, 2002, 2006, 2007). A similar effect was seen for stimuli predicting the non-availability of reward (Matsumoto & Hikosaka, 2007; Tobler et al., 2003, but see also

Matsumoto & Hikosaka, 2009). An inhibitory interpretation of these deactivations might be further supported by studies demonstrating that the voluntary inhibition of cue-evoked craving results in deactivations in brain regions (e.g., the ventral striatum and medial OFC) involved in reward prediction and reward processing (Volkow et al., 2010). Interestingly, the attentional bias to BEGIN stimuli reported by Stippekohl et al. (2012a) was accompanied by mesocorticolimbic deactivations in smokers (e.g., in the ventral striatum and medial frontal cortex). Thus, smokers probably had to inhibit the responses evoked by BEGIN stimuli to accomplish the performance level of non-smokers, which was not required in case of END stimuli. Besides its role in discrimination learning the anterior cingulate cortex is also involved in the detection of conflict (Botvinick, Cohen, & Carter, 2004; Braver et al., 2001; Carter, Botvinick, & Cohen, 1999; Martin-Soelch et al., 2007). Thus, in contrast to BEGIN stimuli, which might have evoked response tendencies incompatible with the experimental context, this response conflict might be minor in case of END stimuli. Although these data are indeed very exciting, they may be partially limited by the motivational baseline used for comparisons, which was defined within-group only. However, this is probably not an uncommon phenomenon in the literature (see, for example, Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010). Interestingly, deprivation had hardly an effect on BEGIN stimuli and apparently resulted in an overall shift of subjective craving only. This lack of an interaction was seen before with cue-modulated startle (Geier et al., 2000, but see also Cinciripini et al., 2006) and was also reported by studies using the cue availability paradigm (Bailey et al., 2010). In contrast, deprivation had a more pronounced effect on END stimuli, which further argues for their distinct properties. Compared to non-deprived smokers END stimuli evoked lower activity in the insula, orbitofrontal and dorsolateral prefrontal cortex of deprived smokers. Moreover, in deprived smokers deactivations in the DLPFC and parts of the OFC were found. Previous studies (Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Wilson et al., 2004) reported reduced activity in these structures particularly in drug users undergoing or seeking treatment (but see also Chase, Eickhoff, Laird, & Hogarth, 2011). In those participants the perceived availability of smoking may be reduced, which would be in line with results from (McBride, Barrett, Kelly, Aw, & Dagher, 2006) who experimentally manipulated the expectancy to smoke. This study found practically no cue-evoked activity when smoking was unavailable for several hours after the experiment. Finally, a recent study addressed the interaction of cue reactivity and smoke availability by combining fMRI

with direct manipulations of neuronal activity via transcranial magnetic stimulation (Hayashi, Ko, Strafella, & Dagher, 2013). This research highlighted the importance of the DLPFC in mediating the effects of smoke availability on cue reactivity. In particular, transient deactivations of the DLPFC diminished the potentiating effects of smoke availability on cue-evoked craving and neuronal activity in structures of the mesocorticolimbic system (e.g., the medial OFC, ACC and ventral striatum).

MECHANISMS UNDERLYING THE REACTIVITY OF TERMINAL STIMULI

Overall, the studies cited above demonstrated that END stimuli differ from BEGIN stimuli regarding to several important aspects. These results seem to be indeed paradoxical given that a stimulus clearly associated with smoking and the nicotine effect fails to evoke the high craving response assumed to be characteristic for smoking cues. Moreover, this research revealed several indications that END stimuli may not just be weak cues for smoking. Instead, they may evoke their own kind of reactivity which may partially oppose the reactivity seen for BEGIN stimuli. Indeed, END stimuli possess several interesting features which set them apart from BEGIN stimuli. First, as the name already implies, these stimuli are related to the completion of smoke intake. Second, it seems obvious that smoke uptake from a finished cigarette is not easily accomplished. Thus, the perceived availability of smoking may be low in case of terminal stimuli. Third, END stimuli show a close temporal relationship to the nicotine peak and the events following the termination of smoking.

The functional significance of terminal smoking stimuli in the control of addictive behavior can be addressed from different theoretical perspectives (for a detailed discussion see Mucha et al., 2008). For example, END stimuli may differ from BEGIN stimuli in terms of their predictive relationship to smoke intake. In contrast to BEGIN stimuli, which may signal high smoke availability, END stimuli may signal poor smoke availability. As mentioned above, there is convincing evidence that the reactivity evoked by "one and the same" smoking cue can be enhanced or decreased if smoking seems available vs. unavailable, respectively. This was shown for cue-evoked craving, positive affect, latency to smoke, electrodermal and neural activity and was even demonstrated in test-paradigms manipulating the probability of gaining access to single puffs on a cigarette (Bailey et al., 2010; Carter & Tiffany, 2001; Dols, van den Hout, Kindt, & Willems, 2002; Droungas et al., 1995; McBride et al., 2006; Wertz & Sayette, 2001). Thus, the poor cue-properties of END stimuli may actually

reflect their signaling of poor smoke availability. Importantly, this hypothesis may provide a further link into a putative inhibitory function of terminal smoking stimuli. From a conditioning perspective the lack of a drug-use opportunity has been hypothesized to function as part of a compound stimulus, as negative occasion setter or conditioned inhibitor to mention only a few possibilities (Holland, 1984; Rescorla, 1969, 1985; Rescorla & Wagner, 1972; Swartzentruber, 1995; Wertz & Sayette, 2001).

Furthermore, the terminal stage of smoking may give rise to conditioning processes contributing to the cessation of drug intake. Drug self-administration frequently occurs in regular patterns (e.g., bouts or binges), followed by a consistent pause after reinforcement (Wise, 1997; Yokel & Pickens, 1974). Thus, END stimuli may be related to a period free of smoking. Although several explanations have been proposed to account for the intermittency of drug seeking and intake behavior (see, for example, Lynch & Carroll, 2001; Norman & Tsibulsky, 2006; Panlilio, Thorndike, & Schindler, 2008) one hypothesis states that the self-administration of a drug will be reinitiated when drug levels fall below an internal "trigger point" - not equitable to a depletion point (see Wise, 1997; Wise & Kiyatkin, 2011; Yokel & Pickens, 1974). Above this threshold the neuronal substrate mediating the rewarding effects may have become "saturated" thereby rendering *further* drug intake non-rewarding (Brody et al., 2009; Brody et al., 2006; Panlilio et al., 2008; Panlilio, Thorndike, & Schindler, 2009). Thus, the contingencies inherent in each act of drug consumption may set the occasion for the availability of drug reward, a mechanisms which may provide the basis of a stimulus control account of drug intake. Accordingly, the stimulus conditions prior to consumption may act as discriminative stimuli controlling drug seeking and intake. As interoceptive drug effects may be dose-dependent, these stimuli may provide information about the level of drug in the system. However, stimuli from other modalities may also qualify, especially when derived from stages of the intake ritual with a unique relationship to the drug effect. Thus, drug seeking may be initiated in the presence of stimuli signaling that the level of drug is below the trigger point. In contrast, END stimuli may be related to the maximum drug effect. Thus, smoking will be terminated as additional drug intake is not rewarding. Interestingly, recent studies suggest that the peripheral, interoceptive stimulus characteristics of a drug interact with the central drug effect on the basis of a (Pavlovian) conditioning mechanism (Lenoir & Kiyatkin, 2011; Lenoir, Tang, Woods, & Kiyatkin, 2013; Wise & Kiyatkin, 2011). Moreover, there is rich evidence that drug states can function as operant discrimina-

tive (Stolerman, 1992; Troisi, LeMay, & Jarbe, 2010; Wooters, Bevins, & Bardo, 2009) or differentially conditioned stimuli (Besheer, Palmatier, Metschke, & Bevins, 2004; Bevins & Palmatier, 2004; Murray & Bevins, 2009). Several studies demonstrated that nicotine can serve as discriminative S^D (Troisi et al., 2010), CS+ (Murray & Bevins, 2009) or positive feature (Palmatier, Peterson, Wilkinson, & Bevins, 2004; Palmatier & Bevins, 2007) for food or sucrose reward, respectively. Importantly, nicotine was shown to act as discriminative S^Δ (Troisi, 2003), CS- (Besheer et al., 2004) or negative feature (Bevins, Wilkinson, Palmatier, Siebert, & Wiltgen, 2006), signaling the non-occurrence of reward after an otherwise reinforced stimulus (for - feature-negative - interoceptive conditioning see also Bevins & Palmatier, 2004; Dworkin, 1993; Goddard, 1999; Jaeger & Mucha, 1990; Siegel, 2005; Troisi & Akins, 2004). Moreover, nicotine used as negative feature in a goal-tracking task was recently shown to pass retardation and summation tests used to probe for conditioned inhibition (Murray et al., 2011; see also Skinner, Martin, Howe, Pridgar, & van der Kooy, 1995, who revealed evidence that morphine trained in a feature-negative taste aversion paradigm can pass the summation test of conditioned inhibition). Interestingly, a recent study with cocaine administering rodents demonstrated an inhibitory effect of an exteroceptive S^Δ signaling the lack of (further) cocaine reinforcement at the "end" of an extended period of self-administration, i.e., when drug levels were high (Mihindou et al., 2013). As expected, cocaine seeking was suppressed when further drug was not available, although the control of the S^Δ was partially decreased by a shift in context. Importantly, the S^Δ almost completely abolished cocaine induced reinstatement of drug seeking. Moreover, this effect was behaviorally specific as reinstatement induced locomotion was apparently unaffected. Thus, even in rodents with a prolonged history of self-administration the ability to inhibit cocaine seeking remains at least partially intact (see also: A primer on conditioned inhibition). Furthermore, current human data point to the capacity of human drug users to inhibit cue-evoked craving under certain circumstances, although the underlying mechanisms may be different (Kober, Kross, Mischel, Hart, & Ochsner, 2010a; Kober et al., 2010b; Volkow et al., 2010). Overall, the studies cited above suggest that the interoceptive stimulus effects of a drug and accompanying exteroceptive stimuli may qualify to acquire conditioned inhibitory properties.

As BEGIN and END stimuli may be differentially predictive for an opportunity to engage in smoking or the reward derived from smoking one may assume that both stimuli can

be dissociated from each other by manipulations of smoke availability. And indeed, there is evidence that in contrast to END stimuli, BEGIN stimuli respond sensitive to a manipulation intended to reduce the perceived availability of smoking (Mucha et al., 2008). This manipulation comprised a no-go symbol, similar to a no-smoking sign, overlaid on BEGIN and END pictures, respectively. For BEGIN stimuli this manipulation affected subjective craving, pleasure and cue-modulated startle in the expected way, i.e., it attenuated cue reactivity. In contrast, END stimuli were apparently less affected by this manipulation. This is what one would assume as END stimuli probably already signal poor smoke availability. A second experiment intended to increase smoke availability by presenting an additional smoking cue (which is actually a signal for smoke intake) in combination with a BEGIN and an END stimulus, respectively. This study partly mirrored the summation procedure commonly used in the learning literature (see below: A primer on conditioned inhibition) to look for putative inhibitory effects of conditioned stimuli (Rescorla, 1969). Interestingly, END stimuli failed to fully summate with the reactivity evoked by BEGIN stimuli, i.e., craving and pleasure were only partially increased. These results may provide further support for a thesis that END stimuli may be probably not simply weak cues or neutral stimuli. Instead, they may evoke their own kind of reactivity which may partially oppose the reactivity of cues. However, there are alternative explanations available, which may account for these results. Thus, it has to be noted that the studies mentioned above used combinations of naturalistic picture stimuli and symbolic manipulations of smoke availability. Accordingly, the results may be constrained by limitations of the test conditions. For example the results of the study modeling summation may also be interpreted in line with other models of information processing, e.g., averaging instead of adding stimulus values (Anderson, 1965). Moreover, presenting a BEGIN stimulus in combination with an END stimulus may have reduced cue reactivity due to incomplete generalization to a stimulus compound (i.e., generalization decrement). Furthermore, END stimuli might have drawn attention away from BEGIN stimuli, which is the argument most commonly mentioned in the classic learning literature (Papini & Bitterman, 1993; Rescorla, 1969; Williams et al., 1992). Although this hypothesis seems unlikely given the well-established attention capturing effect of cues (Field & Cox, 2008), i.e., their high incentive "salience" (Robinson & Berridge, 1993) and the results of Stippekohl et al. (2012a), the possibility remains.

Thus, to overcome several limitations of previous studies converging test methods have to be used to challenge the predictive relationship of BEGIN and END stimuli with smoke reward. Accordingly, it may be informative to experimentally manipulate the association of BEGIN and END stimuli to smoke reinforcement. This was the aim of the second study of this thesis, which was based on the protocol of the first experiment (see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers).

The rationale chosen capitalized on features of the retardation procedure used in the conditioned inhibition literature (Rescorla, 1969; and see below: A primer on conditioned inhibition). This complementary approach tackles alternative explanations of previous results in form of simple attentional or other stimulus integration models. For example, enhanced attentional orienting to END stimuli may actually accelerate conditioning. Thus, retarded conditioning of END stimuli as appetitive signals for smoke intake may further support previous data suggestive of inhibitory response components of terminal stimuli. Interestingly, under some assumptions this approach could also be sensitive in detecting conditioned compensatory responses emerging in the presence of terminal stimuli. As described above, conditioning processes tapping into physiological regulatory systems necessary for the maintenance of homeostasis (Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel, 1975; Siegel et al., 2000) may be especially sensitive to a close temporo-spatial overlap with the drug effect. Thus, terminal stimuli may be ideally suited to acquire conditioned compensatory responses attenuating the physiological arousal induced by nicotine (Clarke, 1987; Gilbert, Dibb, Plath, & Hiyane, 2000; Mucha, Mutz, Stephan, & Pauli, 1996; Niedermaier et al., 1993). Interestingly, these responses might also counteract the physiological arousal in preparation of drug intake or evoked by stimuli eliciting a drug-like, proponent response (Stewart, 1992; Stewart et al., 1984; Stewart & Wise, 1992). Thus, this line of argumentation would point to the presence of at least two separate processes involved in drug reward, which may be differentially expressed in several response systems and engaged by stimuli varying in temporal content (see the discussion of Experiment 2: Smoking stimuli from the beginning and terminal phase of cigarette consumption support the conditioning of different physiological responses).

In sum, drug-associated stimuli are commonly thought to act as cues for drug, i.e., they are assumed to evoke high craving and/or drug intake. Accordingly, it seems imperative to

understand why a stimulus clearly associated with drug fails to evoke the reactivity seen for normal cues. In a series of studies it was consistently shown that stimuli from the terminal stage of the smoking ritual (END stimuli) evoke reactivity different from and even opposite to BEGIN stimuli. This was demonstrated with subjective and objective measures of motivation for drug intake and across manipulations intended to probe the functional significance of terminal stimuli. However, further experiments are necessary to fully evaluate the CS properties of END stimuli and a proposed inhibitory function. Thus, it may be fruitful to examine BEGIN and END stimuli in a test-paradigm using features of the retardation procedure of the classic learning literature. This was the aim of the *second experiment* of this thesis (see Experiment 2: Smoking stimuli from the beginning and terminal phase of cigarette consumption support the conditioning of different physiological responses), which relied on the conditioning paradigm of the first experiment (see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers). Retarded conditioning of END stimuli as CS+ for smoke intake would provide further support for their unique response properties and may complement previous results partially suggestive of an inhibitory function.

A PRIMER ON CONDITIONED INHIBITION

As described above, human research on cue reactivity is strongly anchored in the animal drug-conditioning literature. Commonly, drug stimuli are treated as simple excitatory conditioned stimuli, putatively established by a reliable association with the drug effect. Although recent research has started to address other forms of learning, e.g., the modulatory impact of contextual stimuli on cue reactivity (Bouton, 2000; Conklin, 2006; Conklin, Robin, Perkins, Salkeld, & McClernon, 2008; Thewissen, Snijders, Havermans, van den Hout, & Jansen, 2006; Thewissen, Van Den Hout, Havermans, & Jansen, 2005), the importance of inhibitory stimulus control has been generally neglected so far. In direct contrast, conditioned inhibition is a continuing topic of animal research and theorizing since the origins of the field of associative learning (Pavlov, 1927).

GENERAL THOUGHTS ON INHIBITORY CONDITIONING

Accordingly, it is hardly surprising that theoretical perspectives disagree about the precise content of learning in inhibitory conditioning (Denniston, Savastano, & Miller, 2001; Dickinson & Dearing, 1979; Holland & Coldwell, 1993; Konorski, 1948; Konorski, 1967; Pavlov, 1927; Rescorla & Wagner, 1972; Savastano et al., 1999; Tinsley et al., 2002; Wagner & Brandon, 1989). Although a detailed description of different theoretical notions is far beyond the scope of this thesis, it may be useful to consider one well-known working-definition, which specified a conditioned inhibitor in terms of its relationship to a conditioned excitor. Thus, "a stimulus, then, is called a conditioned inhibitor if, as a result of experience of the organism with some operation relating that stimulus to the US, the stimulus comes to control a tendency opposite to that of the conditioned excitor" (Rescorla, 1969, p. 78). Interestingly, this definition left the precise procedures generating conditioned inhibition open for empirical research, although a negative contingency was later proposed as necessary determinant of inhibitory learning (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972). In dealing with the problem of conditioned inhibition in drug addiction, this analysis suggests the presence of a form of drug stimuli with "anti-cue" properties. Thus, these stimuli may decrease (more precisely: oppose) the responses evoked by excitatory conditioned cues (e.g., craving, positive affect and self-administration of drug). However, conditioned inhibition may not always be exactly symmetrical and mutually exclusive to conditioned excitation (Baker, 1974; Droungas & LoLordo, 1994; Falls & Davis, 1997; Lysle & Fowler,

1985; Rescorla, 2005; Williams & Overmier, 1988; Zimmer-Hart & Rescorla, 1974). Instead, conditioned stimuli may acquire the capacity to modulate (un-) conditioned responses (Bouton, 2004; Domjan, 2005; Holland, 1984; Holland & Coldwell, 1993; Hollis, 1997; Rescorla, 1987; Swartzentruber, 1995), independent from direct excitatory or inhibitory effects. Moreover, if one thinks of conditioning to engage the "organizing and integrating effects" (Bolles & Fanselow, 1980, p. 291) of whole motivational (e.g., appetitive vs. aversive) systems (Dickinson & Dearing, 1979; Konorski, 1967; Timberlake, 2001) on perception and behavior, the preference for a strict symmetry may be swept away by a functional approach on learning (Silva et al., 1998; Timberlake, 2001; Tinsley et al., 2002). Thus, depending on the test situation and the adaptive demand produced by the reinforcer in question, inhibitory conditioned stimuli may sometimes evoke responses opposite to, similar or (qualitatively) different from those evoked by control stimuli and/or the corresponding excitors. One simple example may concern the arousal component of incentive motivation. Considering the reciprocal interaction of appetitive and aversive motivational systems (Dickinson & Dearing, 1979; Dickinson & Pearce, 1977; Konorski, 1967; Lang, Bradley, & Cuthbert, 1992; Lang & Davis, 2006; Weiss, 1978), conditioned excitors and inhibitors of opposite incentive classes were hypothesized previously as functionally equivalent. Thus, an conditioned inhibitor of an aversive motivational state may function as appetitive "safety signal", counteracting the mobilization of defensive responses. Dependent on the test conditions such a CS may energize approach, which may be accompanied by increased arousal[2].

Independent form theoretical conceptualizations this line of reasoning has several implications for the present thesis. First, the reactivity evoked by conditioned inhibitors may be dependent on the specific type of measure used. Thus, not all dependent variables may be equally useful to discriminate between excitatory and inhibitory trained stimuli. Second, (physiological) measures of motivational valence may be suitable to provide a glimpse at the putative motivational organization of conditioned responding. Third, the measurement asymmetry between conditioned excitation and inhibition necessitates the use of specific test procedures. As mentioned above (see: Core features of conditioning and Poor cue effects of terminal smoking stimuli), commonly some degree of excitation has to be present

[2] Concerning arousal, such a stimulus would certainly not qualify as a conditioned inhibitor as characterized by the working definition cited above, although it was obviously *conditioned* (i.e., trained) in an inhibitory paradigm.

to demonstrate inhibition[3]. Thus, to measure a reduction of a response, a response has to be present in the first place. This is the test-logic underlying the summation procedure described above. Alternatively, conditioned inhibition may be expressed as the resistance of a putative inhibitor to excitatory conditioning (retardation test). Furthermore, it may be valuable to use both tests (i.e., the "two-test strategy") to roughly control for simple explanations of apparent inhibition in terms of attentional engagement[4] (Hearst, 1972; LoLordo & Fairless, 1985; Rescorla & Wagner, 1972; Savastano et al., 1999; Williams et al., 1992).

INHIBITORY PROCESSES IN DRUG CONDITIONING

Overall, the animal learning literature provides a rich source of evidence for the importance of inhibitory processes in the control of conditioning responding. Furthermore, recent research has even started to disentangle the underlying neural mechanisms (Christianson et al., 2011; Davis, Falls, & Gewirtz, 2000; Falls, Bakken, & Heldt, 1997; Guillory, Suto, You, & Vezina, 2006; MacLeod & Bucci, 2010; Ostroff, Cain, Bedont, Monfils, & LeDoux, 2010; Tobler et al., 2003). Although inhibitory conditioning is commonly neglected in the animal drug-conditioning literature, there are isolated reports which suggest that core features of addiction - such as tolerance (Fanselow & German, 1982; Hinson & Siegel, 1986; Siegel et al., 1981; Vila & Miranda, 1994), sensitization (Stewart & Vezina, 1991; Vezina & Leyton, 2009) and even overt drug seeking behavior (Kearns et al., 2005; Mihindou et al., 2013; Weiss et al., 2007) can come under inhibitory stimulus control. For example, a famous study conducted by Siegel and colleagues showed that a CS- explicitly unpaired with the application of morphine (i.e., presented four hours after its administration) subsequently retarded the development of morphine conditioned analgesic tolerance in comparison to various controls (Siegel et al., 1981). Interestingly, this "anti-tolerance"-like effect was not present at the beginning of the test-phase, but occurred during later stages of conditioning. Although these results do not necessarily argue against a simple symmetrical account of conditioned inhibition, they at least emphasize the necessity to use appropriate test-procedures to reveal putative inhibitory effects. Furthermore, Fanselow and German (1982) provided

[3] This constraint may be less in bidirectional response systems.

[4] It may be interesting here to ask, if this would be a reasonable approach to deal with conditioned changes in attentional processes (e.g., Bindra, 1978; Mackintosh, 1975; Pearce & Hall, 1980; Robinson & Berridge, 1993; Stewart et al., 1984).

evidence for the retarded acquisition of tolerance to the locomotor suppressing effects of morphine in case of a CS previously trained in an explicit unpaired fashion. Moreover, Hinson and Siegel (1986) reported similar results with another class of drug and response using a differential conditioning paradigm. As expected, conditioned tolerance to the hypothermic effect of pentobarbital developed in presence of the drug-paired CS+, although the CS- evoked no overt hypothermic reaction. However, compared to controls tolerance to a pentobarbital challenge was lowest in case of the former CS-. Finally, Vila and Miranda (1994) showed that a Pavlovian conditioned inhibitor (A+/AX-) reduced tolerance to the adipsic effects of scopolamine when presented in summation with a separately trained transfer excitor. Interestingly, the conditioned inhibitor had no effect on water intake on its own. Overall, these results emphasize the need to consider the impact of inhibitory conditioned stimuli on the expression of drug tolerance in the dependent human.

Moreover, a recent review on the situational-specific expression of psychomotor sensitization discussed the importance of inhibitory processes in the modulation of behavioral sensitization (Vezina & Leyton, 2009). For instance, there is considerable evidence that drug-sensitized animals show no or only weak signs of behavioral sensitization in an environment unpaired (i.e., explicitly unpaired or *never*-paired) with the application of the drug (Anagnostaras & Robinson, 1996; Carey & Gui, 1998). However, after the extinction of context-dependent sensitization (i.e., the context-dependent conditioned response evoked by an injection of saline), sensitized responding to a drug challenge can be found in both, the paired and unpaired context. Thus, extinction of context-dependent sensitization may have abolished the inhibition of sensitization in the (explicitly) unpaired environment (Brabant, Tambour, Quertemont, Ferrara, & Tirelli, 2011; Stewart & Vezina, 1991). This may suggest conditioned inhibition as a "slave process" dependent on conditioned excitation (see, for example, Lysle & Fowler, 1985). Moreover, the disruption of context-dependent drug memories by electroconvulsive shocks (which probably affected the reconsolidation of the reactivated memory trace) revealed robust sensitization in the unpaired context, suggesting that the expression of sensitization was previously inhibited (Anagnostaras, Schallert, & Robinson, 2002). Interestingly, the shocks had no effect on sensitization produced by a drug challenge in the paired context or on the conditioned behavioral response when saline was given in the paired context. Furthermore, evidence from anesthetized rats functioning as "zero-context" control suggests that the lack of sensitization expressed in a context un-

paired with drug may indeed be due to inhibition (Wang & Hsiao, 2003). Overall, these data suggest the presence of an inhibitory mechanism, preventing the expression of sensitization in a context never paired with drug. Stewart and colleagues (see Stewart, 1992; Stewart & Vezina, 1988; Stewart & Vezina, 1991) hypothesized that the inhibition of behavioral sensitization may be due to the negative contingency between the context (CXT-) and the drug (US). Thus, stimuli predictive of the non-occurrence of drug may function as conditioned inhibitors acting on a sensitized unconditioned response. However, several results are apparently problematic for a simple excitatory or inhibitory conditioning account of sensitization – e.g., the inhibition of sensitization in a context *never* paired with drug (see Anagnostaras et al., 2002; Brabant et al., 2011). Thus, the mechanisms involved may be better understood as a form of inhibitory occasion-setting (see Anagnostaras et al., 2002; Brabant et al., 2011). Nevertheless, these studies cited above suggest that addictive drugs can give rise to learning processes which may prevent the expression of sensitization.

Finally, several studies suggest that even overt drug seeking behavior can come under inhibitory stimulus control. Kearns et al. (2005) were probably the first who demonstrated a pronounced reduction of cocaine seeking by a differential (A+/X-) or Pavlovian conditioned inhibitor (A+/AX-) in a summation test. Interestingly, a subsequent study provided evidence for a suppression of cocaine seeking by a Pavlovian conditioned inhibitor signaling the non-availability of food (Weiss et al., 2007). This may suggest that conditioned inhibition of reward seeking generalizes across different incentive classes, which may be indicative of a general reduction of an appetitive motivational state (Dickinson & Dearing, 1979; Konorski, 1967). However, this interpretation might be limited by the absence of controls for response competition[5] and in need for further evaluation, as a subsequent study failed to find any difference in the suppression of cocaine seeking produced by a novel stimulus or a food-based Pavlovian inhibitor (Lombas, Kearns, & Weiss, 2008b). Finally, a recent study of Mihindou et al. (2013) suggest that a discriminative S^{Δ} signaling the non-availability of (further) cocaine reward can recruit inhibitory control mechanisms even in rodents with an extensive history of cocaine self-administration (see also: Poor cue effects of terminal smoking stimuli). Overall, this short synopsis of animal research strongly emphasizes the necessity to consider the involvement of inhibitory stimulus control in human drug addiction.

[5] Sometimes it may be difficult to separate the effects of central – affective-motivational – processes from peripheral response interactions (Dickinson & Pearce, 1977; Weiss, Thomas, & Weissman, 1996).

CONDITIONED INHIBITION IN THE HUMAN LITERATURE

Since the human drug conditioning literature commonly ignores conditioned inhibition, a broader empirical data base has to be considered as an integrative framework for the last experiment of this thesis (see Experiment 3: Conditioned inhibition of subjective and physiological reward-directed responses as indicated by a retardation test). Obviously, appetitive conditioning paradigms would be relevant. However, these are afflicted by the same problem, i.e., a focus constricted on excitatory conditioning (Cox, Andrade, & Johnsrude, 2005; Franken, Huijding, Nijs, & van Strien, 2011; Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010; Mallan & Lipp, 2007; Van Gucht, Vansteenwegen, Van den Bergh, & Beckers, 2008). Probably most of the experimental data on conditioned inhibition in humans is based on the predictive learning of outcome expectancies (Karazinov & Boakes, 2004; Melchers, Wolff, & Lachnit, 2006; Migo et al., 2006; O'Boyle & Bouton, 1996; Urcelay, Perelmuter, & Miller, 2008; Williams, 1995). To the best of my knowledge there are no studies available yet, which probed appetitive conditioned inhibitors with physiological measures of motivational valence. This is actually surprising, given the clear importance of appetitive conditioning processes in the formation and maintenance of clinical disorders (Martin-Soelch et al., 2007), e.g., drug addiction (Robinson & Berridge, 1993; Stewart et al., 1984) or obesity (Petrovich & Gallagher, 2007; Volkow, Wang, & Baler, 2011; Weingarten, 1983). Thus, it is imperative to better understand the contribution of excitatory and inhibitory reward conditioned stimuli to the emergence and maintenance of these disorders, respectively.

In contrast, conditioned stimuli predictive for the absence of an aversive event (safety signals) are increasingly acknowledged in the fear conditioning literature and suggested to be important in the pathogenesis of anxiety disorders (Andreatta et al., 2010; Jovanovic & Ressler, 2010; Lissek et al., 2005; Lohr, Olatunji, & Sawchuk, 2007; Waters, Henry, & Neumann, 2009b). Accordingly, there are several studies with aversive US which probed conditioned inhibition with tests derived from the animal literature. For example, Neumann, Lipp, and Siddle (1997) used a complex training design to induce an elemental stimulus processing strategy, which included, i.a., a mixture of Pavlovian conditioned inhibition (A+/AX-) and differential conditioned inhibition (A+/X-). This study found partial evidence for conditioned inhibition of shock expectancy and skin conductance responses in a summation test. Compared to a neutral control stimulus, the putative inhibitor reduced responding when

presented in compound with a test excitor. In contrast, in a previous study conditioned inhibition of skin conductance failed to exceed external inhibition in a summation test with a novel stimulus (Grings, Carey, & Schell, 1974). Furthermore, Grillon and Ameli (2001) used a serial feature-negative discrimination (A+/X->A-) (see, for example, Holland & Coldwell, 1993) but failed to demonstrate inhibition of skin conductance and startle responses as indexed by a summation test with a transfer excitor. In contrast, Jovanovic et al. (2005) trained participants in a conditional discrimination procedure (AB+/BX-) and reported transfer of fear inhibition as measured by fear-potentiated startle during an AX compound. Overall, these results provide at least partial support for the notion that signals predictive for the absence of an aversive event might act as conditioned inhibitors of a negative motivational state (see also Christianson et al., 2012; Jovanovic et al., 2010; Jovanovic et al., 2009). However, several studies (e.g., Grillon & Ameli, 2001; Jovanovic et al., 2005; Neumann et al., 1997; Williams, 1995) emphasized problems arising from configural learning in Pavlovian conditioned inhibition (i.e., AX- is processed as a stimulus compound) and the assessment of conditioned inhibition with the summation procedure (e.g., successful transfer of inhibition to a test excitor). Thus, the last experiment of this thesis targeted to overcome these problems and to maintain high comparability to the two previous studies of this thesis (see Experiment 3: Conditioned inhibition of subjective and physiological reward-directed responses as indicated by a retardation test). The rational of the study was to experimentally establish and probe reward conditioned inhibition based on the principles of the retardation procedure. This approach may be useful to further our understanding of terminal stimuli and inhibitory stimulus control in drug addiction and human incentive motivation. Commonly, drug cues are treated as simple excitatory conditioned stimuli. In contrast, terminal stimuli may be formed by associative processes connected to the non-availability of smoke intake or reward, as mentioned above (see: Poor cue effects of terminal smoking stimuli). Thus, one may hypothesize that the reactivity evoked by END stimuli mirrors the reactivity of a conditioned appetitive inhibitor. Based on the functional overlap of appetitive conditioned stimuli from different incentive classes (Dickinson & Dearing, 1979; Dickinson & Pearce, 1977; Konorski, 1967; Lang & Davis, 2006; Sescousse, Caldú, Segura, & Dreher, 2013; Weiss, 1978; Wise & Bozarth, 1987), it may be possible to partially emulate BEGIN and END stimuli as reward conditioned excitatory (CS+ or S^D) and inhibitory stimuli (CS- or S^Δ), respectively. Moreover, such an approach would be useful to elucidate the associative architecture under-

lying inhibitory stimulus control of core components of incentive motivation in the human (e.g., positive affect and reward seeking), which is of both theoretical and clinical importance (Green, Chess, Conquest, & Yegla, 2011; Martin-Soelch et al., 2007; Robinson & Berridge, 1993; Stewart et al., 1984; Volkow et al., 2011).

To summarize, drug cues are commonly treated as excitatory conditioned stimuli predictive of the drug and its effect on the organism. Thus, they are assumed to motivate further drug intake, thereby contributing to the maintenance of the disorder. Importantly, the classic learning literature suggests that stimuli predictive of the absence of drug reward may actually inhibit conditioned responding. This line of reasoning argues for the existence of a class of drug stimuli with "anti-cue" properties. Moreover, this raises the question if terminal smoking stimuli can be understood as inhibitory conditioned stimuli, predictive for the non-availability of (further) drug intake or reward. Accordingly, it is imperative to provide evidence for reward conditioned inhibition in the human. This approach may function as integrative framework and convenient means to investigate the mechanisms underlying the reactivity of terminal stimuli and inhibitory stimulus control in drug addiction. Ultimately, such an approach will make several possible confounds inherent in naturalistic picture stimuli and intake situations directly accessible to experimental control. Thus, the *third experiment* of this thesis (see Experiment 3: Conditioned inhibition of subjective and physiological reward-directed responses as indicated by a retardation test) is probably the first which used physiological measures of motivational valence to probe the inhibitory effects of a discriminative S^{Δ} for monetary reward as indexed by retarded conditioning.

Aim of the dissertation

In dealing with the behavioral problem of drug addiction, learning processes are stressed to account for the situational specific expression of core features of the disorder (Everitt & Robbins, 2005; Koob & Le Moal, 2008; Robinson & Berridge, 1993; Siegel et al., 2000; Solomon & Corbit, 1973; Stewart et al., 1984; Wikler, 1948; Wise, 2004). The animal literature highlights the contribution of several forms of drug-conditioned stimuli to the persistence of compulsive drug seeking, even after prolonged periods of extinction (Bossert, Marchant, Calu, & Shaham, 2013; Ciccocioppo et al., 2004; Cohen et al., 2005; Le Foll & Goldberg, 2006). Commonly, drug *cues* are treated as simple excitatory conditioned stimuli promoting *craving* and/or drug consumption (see Drummond, 2001; Mucha et al., 2008). However, there is considerable evidence that the perceptual, physiological and behavioral effects of conditioned stimuli may be dependent on the temporo-spatial relationship to the unconditioned stimulus (Bindra, 1974; Domjan, 2005; Fanselow, 1997; Timberlake, 2001). Thus, drug stimuli may be differentially prone to support the responses necessary for the preparation, consumption and physiological adaptation to the drug (e.g., Mucha et al., 1999). Furthermore, the nature of the conditioned response may be determined by the presence of additional (contextual) stimuli (Bouton, 2000; Conklin, 2006; Domjan, 2005; Kearns et al., 2005 ; Panlilio et al., 2000; Thewissen et al., 2005; Timberlake, 2001), which may provide information about the availability of the reinforcer. According to classic learning theories (Hearst, 1972; Konorski, 1967; Pavlov, 1927; Rescorla, 1969; Savastano et al., 1999), stimuli predictive of the non-availability of drug may acquire "anti-cue" properties, opposing the responses of a given drug and drug-related cues (Kearns et al., 2005; Mihindou et al., 2013; Siegel et al., 1981; Stewart & Vezina, 1991; Vezina & Leyton, 2009; Vila & Miranda, 1994). Thus, from a theoretical, methodological and clinical perspective it is imperative to better understand the precise mechanisms determining drug-conditioned responding.

According to incentive theories (Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987), drug cues are hypothesized to be appetitive in nature evoking a tendency to seek out and consume a drug. Although studies with naturalistic smoking cues provide at least partial evidence for this assumption (e.g., Bailey et al., 2010; Carter & Tiffany, 2001; Drobes & Tiffany, 1997; Franklin et al., 2007; Geier et al., 2000), they necessarily have to be

silent about whether this reactivity is actually the result of conditioning (Robbins & Ehrman, 1992). Further support for this assumption comes from studies which experimentally manipulated the conditioning process in humans (e.g., Lazev et al., 1999; Mucha et al., 1998). However, evidence for appetitive smoke conditioned responses with physiological measures of motivational valence is scarce. Moreover, smoking stimuli are thought to increase smoke intake, which is most commonly assessed by measuring the influence of cues on the topography of smoking (e.g., Hogarth et al., 2010; Payne et al., 1991; Surawy et al., 1985). Thus, one can hypothesize that smoke-paired stimuli acquire the capacity to evoke motor activity in anticipation of the consummatory response (i.e., puffing on a cigarette, see below). Accordingly, the aim of the *first experiment* of this thesis was to test these hypotheses by experimentally paring artificial stimuli with smoke intake in the lab to provide support for the conditioning of preparatory and consummatory responses.

The *second experiment* adapted this paradigm to answer the question if the nature of the conditioned response is dependent on the temporal position of the conditioned stimuli in the intake ritual. Previous research provided considerable evidence that stimuli from the terminal stage of cigarette consumption (END stimuli) fail to evoke the reactivity characterizing normal smoking cues (Mucha et al., 2008), i.e., stimuli prior to or from the beginning of consumption (BEGIN stimuli). Importantly, several lines of evidence suggest that END stimuli may not just be weak cues for smoking, but may evoke reactivity different from and partially opposite to the reactivity evoked by BEGIN stimuli (Bushnell et al., 2000; Mucha et al., 2008; Mucha et al., 1999; Mucha et al., 2006; Stippekohl et al., 2012a; Stippekohl et al., 2010). Further support for this assumption stems from previous work showing that BEGIN and END stimuli can be dissociated from each other by manipulations of smoke availability (Mucha et al., 2008). One of these studies was partially conducted in analogy to a summation test used in the classic learning literature to probe putative inhibitory effects of conditioned stimuli. Interestingly, END stimuli decreased the craving and pleasure response to BEGIN stimuli, when presented side by side. Although this would be in accordance with terminal stimuli being inhibitory, there are several limitations tackling this assumption (see above). Thus, to overcome alternative explanations, the second study of this thesis capitalized on features of a retardation test and experimentally manipulated the predictive relationship of BEGIN and END stimuli to smoke reinforcement. In contrast to BEGIN stimuli, attempts to establish END stimuli as excitatory conditioned smoking cues were hypothe-

sized to result in retarded conditioning. This may provide additional support for the notion that the expression of cue reactivity is dependent on the temporal stage of smoking. Furthermore, this may emphasize the importance to consider putative inhibitory effects of smoking stimuli, which may emerge as the result of associative processes tied to the non-availability of smoke intake or reward.

Thus, the aim of the *third experiment* of this thesis was to provide evidence for reward conditioned inhibition in the human, as indexed by retarded excitatory conditioning. As the motivational effects of appetitive conditioned stimuli may be partially comparable (Dickinson & Dearing, 1979; Konorski, 1967; Sescousse et al., 2013; Weiss, 1978; Wise & Bozarth, 1987), such an approach may be valuable for both our understanding of terminal stimuli and inhibitory stimulus control in drug addiction and human incentive motivation. Thus, BEGIN and END stimuli were emulated as discriminative S^D and S^Δ for monetary reward, which provided an efficient and convenient mean to investigate the putative learning process underlying an inhibitory conditioning notion of terminal stimuli. Moreover, this study critically extends previous animal (Davis et al., 2000; Falls & Davis, 1995; Josselyn, Falls, Gewirtz, Pistell, & Davis, 2005) and human data (Christianson et al., 2012; Jovanovic et al., 2005; Jovanovic et al., 2009) based on work with aversive reinforcers, indicating conditioned inhibition of overt defensive responses as measured by fear-potentiated startle. In contrast to previous non-aversive (e.g., prediction tasks with "neutral" outcomes; see, for example, Melchers et al., 2006; Migo et al., 2006; Williams, 1995) and appetitive causal learning tasks (He, Cassaday, Howard, Khalifa, & Bonardi, 2011), the third study of this thesis targeted reward conditioned changes in three affective response systems: subjective report, physiological responses and overt behavior (see Lang, Bradley, & Cuthbert, 1998; Mauss & Robinson, 2009). This approach allows to provide ”proof of concept” (see, for example, Hogarth, Dickinson, Hutton, Bamborough, & Duka, 2006a; Panlilio et al., 2008; 2009, for studies following this approach) of a mechanism supposed to give rise to drug conditioned inhibition by modeling core features of drug reward (appetitive motivation and reward seeking). Ultimately such an approach may be useful to elucidate the associative architecture underlying stimulus control in clinical disorders like drug addiction, where the processing of reward and reward-related stimuli probably has gone astray.

All studies of this thesis included subjective and physiological measures of conditioned responding. Subjective pleasure and arousal were assessed as partially independent indices

of the directing and activating effects of incentive-motivational stimuli. It was demonstrated repeatedly, that several emotions can be organized on these partially independent bipolar dimensions (Lang & Davis, 2006; Osgood, Suci, & Tannenbaum, 1957; Wundt, 1896). Craving as subjective core component of motivation for drug was measured in the smoke conditioning studies (Carter & Tiffany, 1999; Drummond, Litten, Lowman, & Hunt, 2000). Besides, contingency awareness was tested as a putatively important determinant of conditioning in humans (Lovibond & Shanks, 2002). Facial EMG was chosen as physiological measure of motivational valence. In contrast to affect-modulated startle, spontaneous EMG activity can be measured unobtrusively, which avoids problems arising from aversive stimulation during appetitive conditioning. Previous research demonstrated the M. zygomaticus major ("smiling muscle") and M. corrugator supercilii ("frowning muscle") to be sensitive indices of motivational valence (Bradley, Codispoti, Cuthbert, & Lang, 2001; Dimberg, 1997; Lang, Greenwald, Bradley, & Hamm, 1993; Larsen, Norris, & Cacioppo, 2003). Additionally, in the third study of this thesis activity from the M. orbicularis oculi ("producing crow´s feet") was recorded to enhance the sensitivity of facial EMG to capture muscular main components involved in the generation of a true, authentic Duchenne smile (Darwin, 1872, Duchenne, 1862/1990; Ekman, Davidson, & Friesen, 1990). M. orbicularis oris superior (the upper lip muscle) was selected to assess motor activity in anticipation of the consummatory response (first and second study), i.e., puffing on a cigarette (Müller, Mucha, & Pauli, 2003). Finally, skin conductance was recorded, which is probably one of the most frequently used physiological measures in cue reactivity studies (Carter & Tiffany, 1999). This variable was hypothesized to capture autonomic arousal and orienting in preparation for action (Bradley, 2009; Venables & Christie, 1980). Overall, several studies demonstrated previously that both subjective and physiological variables are susceptible measures of conditioning and motivational processing (Armel, Pulido, Wixted, & Chiba, 2009; Bradley & Lang, 2000; Brown & Schwartz, 1980; Bunce, Bernat, Wong, & Shevrin, 1999; Diesch & Flor, 2007; Dimberg, 1990; Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Flor et al., 1996; Guthrie & Bryant, 2006; Hermann, Ziegler, Birbaumer, & Flor, 2000; Hofmann et al., 2010; Hogarth et al., 2003a; Lang et al., 1990; Larsen et al., 2003).

In sum, the aim of the current thesis was to enhance our understanding of the reactivity evoked by smoking stimuli by 1) providing evidence for the conditioning of appetitive and consummatory physiological responses to a neutral stimulus paired with smoke reward 2)

investigating the CS properties of BEGIN and END stimuli by pairing them experimentally with smoke intake to provide evidence for retarded excitatory conditioning in case of END stimuli 3) strengthening an inhibitory conditioning notion of END stimuli by revealing evidence for reward conditioned inhibition in the human as indexed by a retardation test.

EXPERIMENT 1: CONDITIONED CUES FOR SMOKING ELICIT APPETITIVE AND CONSUMMATORY RESPONSES IN HEALTHY SMOKERS

AIM OF THE FIRST EXPERIMENT[6]

Drug addiction is a chronic relapsing disorder, characterized by compulsive drug seeking and intake (Le Moal & Koob, 2007; Piasecki, 2006). Learning processes are stressed to account for the situational specificity of core features of the disorder, e.g., craving for drug, tolerance, excessive intake and relapse in former addicts. Stimuli accompanying drug intake are proposed to elicit a multitude of drug-conditioned responses (Baker et al., 2004; Eikelboom & Stewart, 1982; Everitt & Robbins, 2005; Koob & Le Moal, 2008; Robinson & Berridge, 1993; Siegel, 1975; Solomon & Corbit, 1973; Stewart et al., 1984; Vezina & Leyton, 2009; Wikler, 1948). According to incentive theories, drug-conditioned stimuli acquire the ability to excite an appetitive central motivational state (Bindra, 1978; Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987). Thus, they are hypothesized to elicit preference and approach and even consummatory behavior.

In human research, the reactivity to drug stimuli is most commonly assessed under the framework of the cue reactivity paradigm. Smoking cues are seen as drug-conditioned stimuli possessing the capacity to evoke craving and smoke intake. Previous research with subjective and physiological measures of motivational valence (e.g., cue-modulated startle and facial EMG of the corrugator and zygomatic muscle) revealed at least partial evidence for an appetitive nature of cue-evoked responding (Cinciripini et al., 2006; Dempsey et al., 2007; Drobes & Tiffany, 1997; Elash et al., 1995; Geier et al., 2000; Griffin & Sayette, 2008; Mucha et al., 2008; Mucha et al., 2006; Muñoz et al., 2011; Orain-Pelissolo et al., 2004; Stippekohl et al., 2010). However, obviously these studies are unable to proof that the reactivity evoked by naturalistic smoking stimuli is the result of conditioning (Robbins & Ehrman, 1992). Accordingly, it is essential to experimentally model the hypothesized conditioning process in the lab to reveal further support for the involvement of appetitive conditioning processes in the formation of smoking cues in humans. Overall, previous smoke-

[6] A modified version of this study has been published by the author of this thesis as Open Access Article (http://creativecommons.org/licenses/by-nc/4.0/) in *Psychopharmacology* and is presented here with minor changes: Winkler, M.H., Weyers, P., Mucha, R.F., Stippekohl, B., Stark, R., & Pauli, P. (2011). Conditioned cues for smoking elicit preparatory responses in healthy smokers. *Psychopharmacology*, 213(4), 781-789. doi: 10.1007/s00213-010-2033-2

conditioning studies only revealed hints for appetitive conditioned responding (Hogarth & Duka, 2006; Lazev et al., 1999; Mucha et al., 1998). Importantly, these results are in need for further support from physiological measures of motivational valence, which have been generally neglected so far. Furthermore, smoking cues are hypothesized to motivate consummatory intake behavior. Previous studies demonstrated that conditioned smoking cues increase both motor activity in preparation for smoking (as indexed by EMG of the trapezius muscle) and actual puffing on a cigarette (Hogarth et al., 2010; Mucha et al., 1998). Thus, it is imperative to provide further support for the conditioning of motor activity involved in the consummatory act of smoking.

Thus, the aim of the first experiment of this thesis as described below was to test these hypotheses by pairing artificial stimuli with smoke intake. The protocol was partially based on previous studies (Hogarth et al., 2003a; Lewin et al., 1986). Smokers participated in a differential conditioning paradigm with single puffs on a cigarette as US and artificial stimuli as CSs. Electromyographically recorded activity of the M. zygomaticus major ("smiling muscle") and M. corrugator supercilii ("frowning muscle") was used as physiological index of motivational valence (Lang et al., 1993). As Müller et al. (2003) suggested the activity of the M. orbicularis oris (lip muscle) as reliable and valid index of puffing on a cigarette, EMG recorded over this muscle was used as measure of motor activity in anticipation of smoking. Skin conductance responses were assessed as indicator of autonomic arousal and orienting in preparation for action (Bailey et al., 2010; Bradley, 2009; Carter & Tiffany, 2001; Hogarth et al., 2003a). Finally, the CSs were rated during the experiment in terms of craving, valence, arousal and contingency awareness. The smoke-associated CS+ was hypothesized to increase subjective craving, pleasure and arousal. Furthermore, conditioning was assumed to result in CS+ evoked skin conductance responses, enhanced activity of the M. zygomaticus major and M. orbicularis oris and reduced activity of the M. corrugator supercilii.

MATERIALS AND METHODS

PARTICIPANTS

Forty-five participants (students) were recruited at the University of Würzburg. They provided written informed consent prior to the study, which was approved by the ethical committee of the German Psychological Association (DGPs, Deutsche Gesellschaft für Psychologie) and was carried out in accordance with the ethical standards of the fifth revision of the Declaration of Helsinki.

Participants were included if they smoked an average of at least 10 cigarettes per day for at least one year and agreed to abstain from smoking two hours prior to the experiment. Exclusion criteria were an age under 18 or above 40 years, a major somatic or psychiatric illness or self-reported consumption of alcohol or illicit drugs before the experiment. Subjects were paid 20 euros for their participation. In addition, the participants received the monetary equivalent of the cigarettes they smoked during the study, which were provided by themselves. Three recruited subjects had to be excluded from the study because of a high number of artifacts in the psychophysiological recording. Three participants were dropped because of absent contingency-awareness (see Results).

Therefore the results are based on the data of 39 subjects (15 male and 24 female). The mean age of the sample was 24.36 years (*SD* = 3.73). Subjects reported regular smoking for 6.63 years (*SD* = 3.07) and consumed 13.39 (*SD* = 3.28) cigarettes per day on average. The mean score on the Fagerström Test for Nicotine Dependence (FTND, Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was 3.19 (*SD* = 1.53). The score on Scale 1 (intention and desire to smoke and anticipated pleasure) of the German version of the Questionnaire on Smoking Urges (QSU-G, Müller, Mucha, Ackermann, & Pauli, 2001) was 4.26 (*SD* = 1.25), the score on Scale 2 (urge to smoke and anticipated withdrawal-relief) was 2.38 (*SD* = 1.12).

STIMULUS MATERIAL

Unconditioned stimulus. One or two puffs on the subjects' preferred brand of cigarettes served as unconditioned stimulus. We allowed the subjects to choose by themselves how often (once or twice) and how deep they liked to inhale because of two reasons: First, the application of the maximum puff number during the experiment may result in high smoke intake (Morris & Gale, 1994; Schupp, Mucha, & Pauli, 1999), which might render smoking

aversive. Second, motivational differences between self-administered and yoked delivery of drug have been reported previously (Twining, Bolan, & Grigson, 2009). The cigarettes were provided by the participants. They were put in a bowl and were placed in a plastic box, together with an ashtray and a lighter. It could be opened on the front. The box was placed on the side of the dominant hand of the subject, approximately 30 cm besides the monitor on which the CSs were presented (see next paragraph).

Conditioned stimuli. Conditioned stimuli (see Figure 1, stimuli not to scale) were modified versions of pictures (picture B and C) used in previous studies (e.g., in Hogarth, Dickinson, Hutton, Elbers, & Duka, 2006b). The pictures used as CS+ and CS- were counterbalanced between the subjects. They were displayed on a white background in the center of a 17 inch color screen (1024 x 768 pixels) placed about 70 cm in front of the subjects.

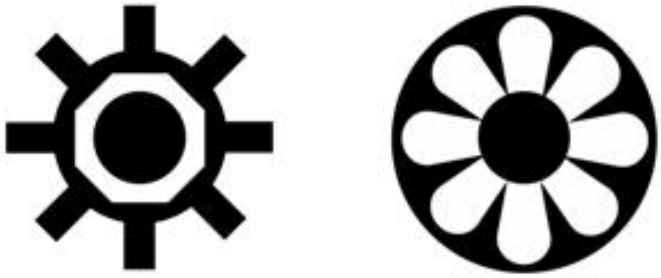

Figure 1 Stimuli counterbalanced between subjects in the role of CS+ and CS- during the conditioning phase.

QUESTIONNAIRES

The Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991) was used as self-report measure of nicotine dependence. The Questionnaire on Smoking Urges (QSU, Müller et al., 2001) was used to assess baseline craving. It consists of several questions on desire to smoke and anticipated pleasure as well as anticipated relief from withdrawal. Self-Assessment-Manikins (SAM, Lang, 1980) were used to document changes in momentary pleasure and arousal during the experiment. The manikins are graphic figures visualizing different values of emotional reactions on the dimensions of pleasure and arousal. For pleasure the poles are visualized by a smiling, happy figure and a frowning, unhappy figure, respectively. For arousal the poles are visualized by a wide-eyed, aroused figure and a sleepy, relaxed figure, respectively. Changes in momentary desire to smoke, eat, drink water or alcohol (not at all - high) were assessed using nine-point scales (see Mucha et al., 1999).

PROCEDURE

After arrival at the laboratory, participants completed a socio-demographic questionnaire, including questions on smoking-related activities and filled in the QSU-G. Next, the motivational state of the subjects was assessed using the questionnaires described above and an alveolar carbon monoxide (CO) sample was taken using a Bedfont Micro Smokerlyzer. After preparation for psychophysiological recording, subjects were seated comfortably in a chair and the computer-assisted part of the experiment was started. The experimental protocol was controlled by Presentation software (Neurobehavioral Systems, Inc.). During a preconditioning phase each CS was presented six times, to habituate putative unconditioned responses to the CSs. The trial-sequence was pseudorandomized, with the constraint of no more than two successive trials of the same CS. Stimuli were presented for 28 s, preceded by a fixation cross for 1.5 s. CS presentation was followed by a 60 s intertrial interval.

At the end of the preconditioning phase each CS was presented again under free-viewing conditions and subjects rated their evoked craving (not at all – high), pleasure (unpleasant – pleasant) and arousal (relaxed – aroused) on 9-point scales appearing on the screen after picture presentation. Next, subjects were informed that in the following part of the experiment sometimes during stimulus presentation a sentence would appear on the screen which would ask them to smoke. In this case they should open the box, light a cigarette and take one or two puffs. After that they should butt out the cigarette, put the smoking paraphernalia back into the box and finally close the box. To ensure that the subjects understood the procedure one supervised CS+ trial as well as one supervised CS- trial followed. If the participants had no further questions the first block of the conditioning phase started, containing 12 CS+ and 12 CS- trials,. Stimulus presentation parameters were the same as during the preconditioning phase, with the exception that during CS+ trials a text appeared on the screen above the CS+ 8 s after stimulus onset and asked subjects to smoke. The first conditioning block ended with the assessment of CS evoked craving, pleasure and arousal as described above. In addition, after presentation of the CSs subjects had to indicate, if they were allowed to smoke during presentation of this picture during the last block (yes/no). Next, the second measurement of breath CO and self-reported motivational state followed. After a short break of 5 minutes, a second identical conditioning block was run. The experiment ended with the third assessment of CO and self-reported motivational state. Overall the study lasted about 2.5 hours.

DATA RECORDING

Psychophysiological activity was recorded continuously by a Vitaport II system (Becker Engineering, Karlsruhe, Germany). Facial EMG was recorded over the left corrugator supercilii and zygomaticus major muscle (according to Fridlund & Cacioppo, 1986) and over the orbicularis oris muscle (according to Müller et al., 2003) using Ag/AgCl miniature electrodes (Ø = 5 mm). Impedance was kept below 10 kOhm. Sampling was at 512 Hz with online high- and low-pass filter settings of 0.015 and 2190 Hz, respectively. The signals were rectified, integrated and stored at 16 Hz (corrugator and zygomaticus) and 256 Hz (orbicularis oris), respectively. EMG of the orbicularis oris was smoothed offline (using a time window of 150 ms). Skin conductance was measured with two Ag/AgCl electrodes (Ø = 8 mm), filled with a 0.05 molar sodium chloride electrolyte paste. Electrodes were placed on the thenar and hypothenar eminences of the non-dominant hand. The Vitaport II system constantly delivered 0.5 V across the two electrodes and sampled skin conductance at a rate of 16 Hz.

DATA REDUCTION AND STATISTICAL ANALYSIS

EMG activity is expressed as the difference between the mean activity during the 8 s after CS onset and the mean activity during the second before each CS presentation. The skin conductance response (SCR) was scored as the largest increase between 1.0 and 6.5 s after CS onset compared to the 1 s baseline mean activity. Responses less than 0.01 µS were scored as zero. Before statistical analysis the logarithms of the SCR-values (SCR + 1) were calculated to normalize the distribution (Venables & Christie, 1980). Scores for each CS were generated by computing the mean of all trials during the preconditioning phase as well as during the first and the second block of the conditioning phase, respectively. Subjective and physiological data of the preconditioning and conditioning phase were analyzed separately. Reported are the Pillai-Bartlett trace statistics of the multivariate approach (Keselman; Keselman, Algina, & Kowalchuk, 2001; Stevens, 2002). Paired t-tests were used to test for differences between the two CSs before training. Data of the conditioning phase were analyzed with two-way repeated measures ANOVAs with CS (CS+ vs. CS-) and conditioning block (Block 1 vs. Block 2) as factors. Alpha level was set at $p = .05$ (two-tailed).

RESULTS

MANIPULATION CHECK

An analysis of the alveolar carbon monoxide levels (see Table 1) confirmed that subjects followed the instruction and really inhaled smoke from the cigarette. $F(2,37) = 49.32$, $p < .001$, $\eta_p^2 = .73$. Compared to the beginning of the experiment carbon monoxide levels were elevated after the end of the first conditioning block, $t(38) = 7.29$, $p < .001$. After the end of the second conditioning block carbon monoxide levels were higher compared to both the beginning of the experiment and the end of the first conditioning block, $t(38) = 9.61$, $p < .001$, vs. $t(38) = 8.62$, $p < .001$, respectively.

Table 1 Breath CO (ppm) and ratings of pleasure, arousal, hunger, thirst and craving for cigarettes and alcohol, respectively (scale-range: 1-9) *before* preconditioning and *after* the first and second block of conditioning [*M* (*SD*)].

	Preconditioning	**Conditioning 1**	**Conditioning 2**
CO	6.23 (8.32)	12.44 (8.41)	16.77 (8.67)
Craving (Cig.)	5.50 (1.92)	3.06 (1.56)	2.81 (1.83)
Pleasure	6.46 (1.23)	5.95 (1.86)	6.36 (2.13)
Arousal	3.20 (1.54)	3.08 (1.90)	3.05 (1.78)
Hunger	3.45 (2.17)	4.45 (2.53)	5.01 (2.55)
Thirst	5.47 (1.74)	6.62 (2.19)	6.78 (1.50)
Craving (Alc.)	1.36 (0.38)	1.46 (0.65)	1.37 (0.52)

CHANGES IN MOTIVATIONAL STATE DURING THE STUDY

There were no significant changes in self-reported pleasure, arousal or desire to drink alcohol, (see Table 1). Overall, subjects felt rather pleasant and relaxed during the experiment. As expected cigarette craving decreased during the study, $F(2,37) = 25.70$, $p < .001$, $\eta_p^2 = .58$. Compared to the beginning of the experiment cigarette craving was lower after the first, $t(38) = 6.94$, $p < .001$, and second block of the conditioning phase, $t(38) = 7.00$, $p < .001$. Instead, desire to eat showed an increase, $F(2,37) = 11.12$, $p < .001$, $\eta_p^2 = .38$. Compared to the beginning of the experiment desire to eat was higher after the first conditioning block, $t(38) = 3.61$, $p = .001$. After the second conditioning block desire to eat was increased compared

to both the beginning of the experiment and the first block of conditioning, $t(38) = 4.76$, $p < .001$ vs. $t(38) = 2.95$, $p = .005$, respectively, of the conditioning phase. Desire to drink water also increased during the experiment, $F(2,37) = 10.60$, $p < .001$, $\eta_p^2 = .36$. Compared to the beginning of the experiment desire to drink water was higher after the first, $t(38) = 3.58$, $p = .001$, and after the second conditioning block, $t(38) = 4.57$, $p < .001$.

CONTINGENCY AWARENESS

Contingency awareness was assessed because human studies on aversive (Lovibond & Shanks, 2002) and smoke conditioning (Hogarth & Duka, 2006) suggest that awareness may be necessary for conditioning (but see also Hamm & Vaitl, 1996). Subjects were defined as aware of the experimental contingency if they were able to correctly report the CS+ and CS- at least at the end of the second conditioning block. Three subjects lacked contingency awareness and were excluded from further analyses. 74.4% of the remaining subjects (i.e., 10 participants) showed contingency awareness after the first conditioning block and 100% after the second conditioning block.

RATING DATA

The analyses of the preconditioning phase revealed no significant effect. In contrast to the hypotheses there were no reliable effects of cue-evoked subjective craving, pleasure or arousal during the conditioning phase (see Table 2).

Table 2 Ratings of craving, pleasure and arousal (scale-range: 1-9) in response to CS+ and CS- *after* pre-conditioning and *after* the first and second block of conditioning [*M* (*SD*)].

		Preconditioning	**Conditioning 1**	**Conditioning 2**
Craving	CS+	5.74 (2.17)	3.10 (2.14)	2.74 (2.20)
	CS-	5.74 (2.25)	2.85 (2.03)	2.92 (2.28)
Pleasure	CS+	5.97 (1.91)	6.23 (2.32)	6.15 (2.25)
	CS-	5.46 (2.29)	5.56 (2.26)	6.15 (2.03)
Arousal	CS+	3.44 (1.97)	3.10 (1.85)	3.05 (1.99)
	CS-	3.56 (2.00)	3.36 (2.02)	3.15 (1.86)

PHYSIOLOGICAL DATA

Skin conductance responses. Skin conductance responses to the CSs did not differ prior to conditioning. An analysis of the data of the conditioning phase revealed a significant main effect of CS, $F(1,38) = 7.49$, $p = .009$, $\eta_p^2 = .17$. As expected, skin conductance responses to the CS+ were stronger than those to the CS- (see Figure 2).

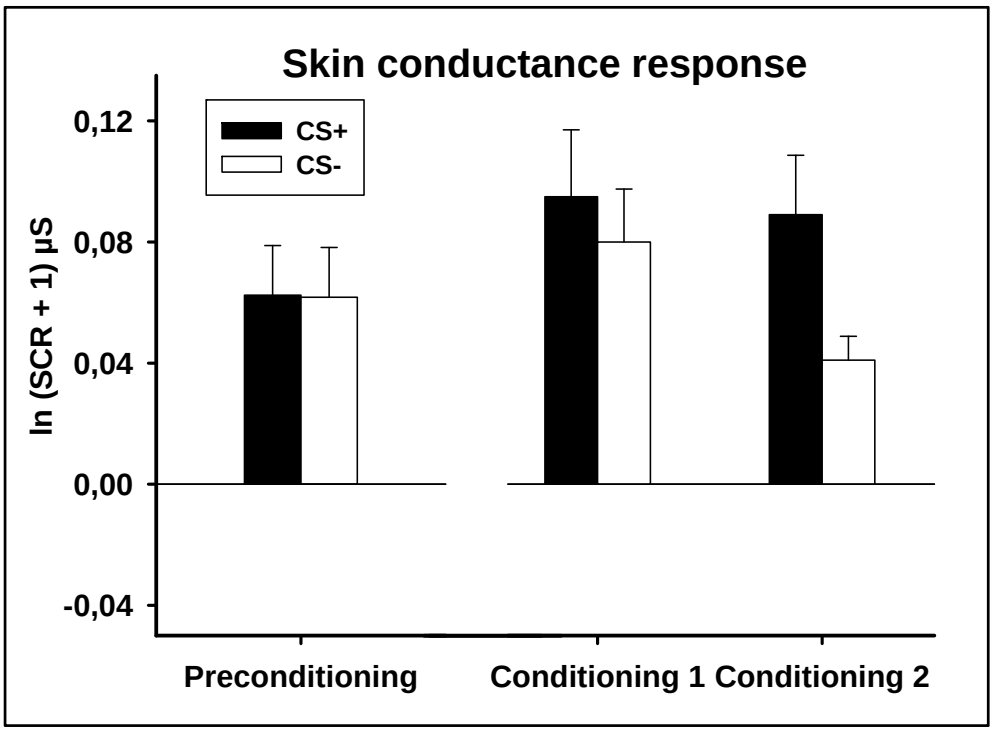

Figure 2 Skin conductance responses [ln (SCR+1)] in response to CS+ and CS- during preconditioning, during the first and during the second block of conditioning [*M* (*SE*)].

M. corrugator supercilii. Neither the analysis of the preconditioning phase nor the analysis of the conditioning phase revealed significant effects.

M. zygomaticus major. There was no difference between the CSs during the preconditioning phase. The analysis of the conditioning phase revealed a significant main effect of CS, $F(1,38) = 6.66$, $p = .014$, $\eta_p^2 = .15$. As expected, the CS+ elicited stronger activity than the CS- during conditioning (see Figure 3). In addition, there was a significant main effect of Block, $F(1,38) = 5.76$, $p = .021$, $\eta_p^2 = .13$. Overall, zygomatic activity was increased during the second conditioning block.

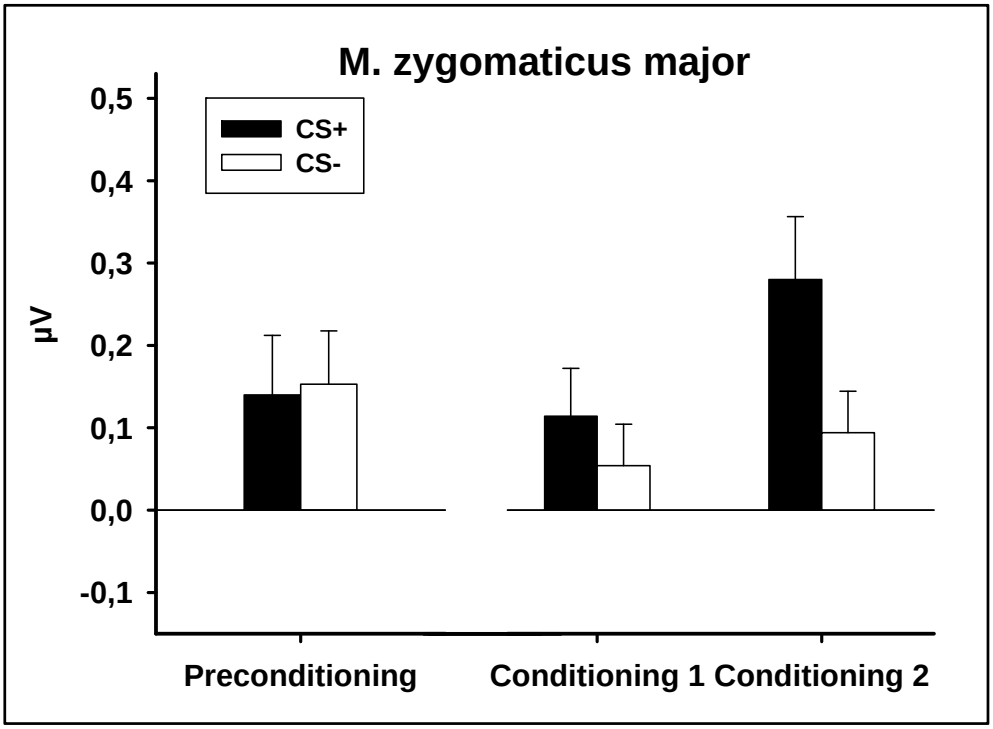

Figure 3 Change in EMG activity (µVolt) of the M. zygomaticus major in response to CS+ and CS- during preconditioning, during the first and during the second block of conditioning [*M* (*SE*)].

M. orbicularis oris. EMG-activity did not differ between the CSs during the preconditioning phase. An analysis of the conditioning phase revealed a significant main effect of CS, $F(1,38) = 4.13$, $p = .049$, $\eta_p^2 = .10$, which was due to higher activity during presentation of the CS+ (see Figure 4).

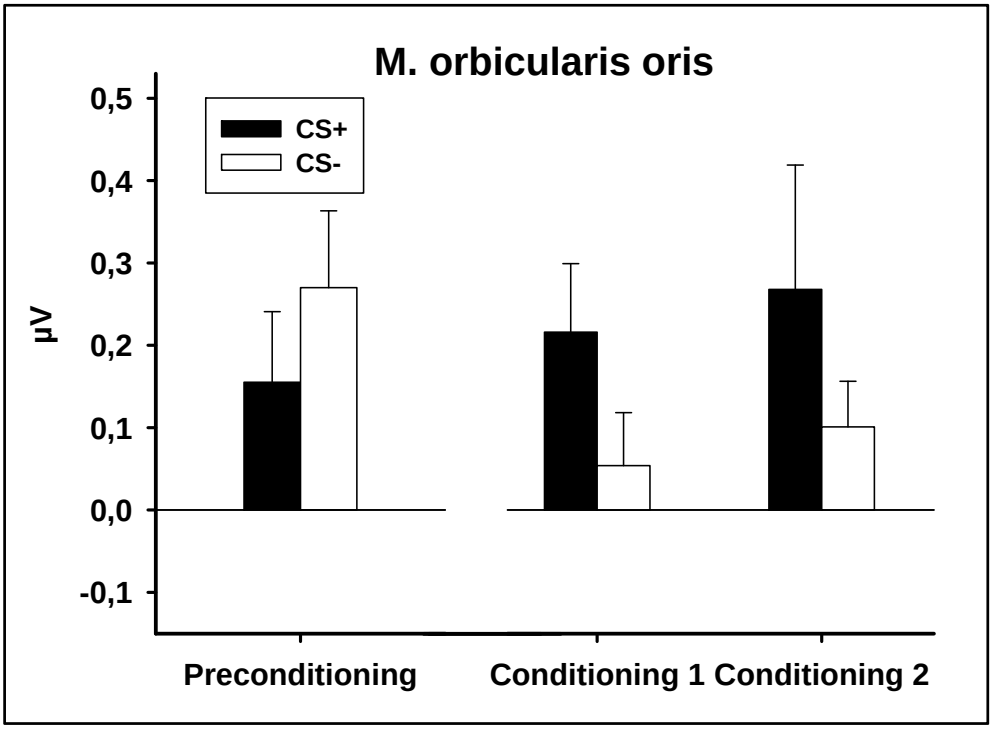

Figure 4 Change in EMG activity (µVolt) of the M. orbicularis oris in response to CS+ and CS- during preconditioning, during the first and during the second block of conditioning [*M* (*SE*)].

DISCUSSION

The present study investigated the development of conditioned responses evoked by an experimentally produced cue for smoking. The study was conducted on healthy smokers and used a differential conditioning protocol, which allowed to control for sensitization (i.e., increased CS evoked responding due to mere exposure to the CS) and pseudoconditioning (i.e., increased CS evoked responding due to mere exposure to the US). Abstract pictorial stimuli served as CSs and single puffs on a cigarette as US (see also Hogarth et al., 2003a). An important feature of the present study was the use of physiological measures of motivational valence which were not included in previous studies.

This study revealed clear evidence for conditioned physiological responses to the smoking cue. During conditioning the CS+ evoked larger skin conductance responses than

the CS-, indicative of increased autonomic arousal and attentional orienting in preparation for action (Bradley, 2009). Furthermore, these data are in line with previous results of Hogarth et al. (2003a). These authors showed that at the end of training a discriminative S^D for smoke reward evoked larger skin conductance responses than the S^Δ. In addition, the magnitude of the skin conductance response was correlated with an attentional bias for the S^D as assessed with a dot-probe task. Furthermore, these results are in accordance with studies showing that naturalistic smoking cues evoke increases in skin conductance (Carter & Tiffany, 1999), which are further modulated by drug availability (Bailey et al., 2010; Carter & Tiffany, 2001). Interestingly, at first glance the present data seem to be inconsistent with predictions derived from compensatory response conditioning, which stress the existence of an adaptive mechanism counteracting the physiological arousal produced by smoking. Thus, heightened autonomic arousal as indicated by enhanced skin conductance would be more in line with assumptions of incentive theories proposing a drug-like, "proponent" response (Stewart, 1992; Stewart et al., 1984; Stewart & Wise, 1992). However, the design of the current study may have been not ideally suited to unmask the existence of conditioned compensatory responses, which may for instance be revealed by manipulations of the CS characteristics (e.g., by the application of stimuli differentially prone to support this form of conditioning, like stimuli from different stages of the smoking ritual or from different modalities), the US characteristics (e.g., by manipulations of the dose per application, as conditioned compensatory responses may be formed by the peak of nicotine) or the use of specific (challenge) tests (e.g., by measuring the modulatory impact of the CS+ on smoking induced arousal or by presenting the CS+ under conditions of deprivation and extinction). Thus, the present paradigm may be fruitfully applied to probe the functional significance of stimuli from the terminal stage of smoking. As stated above, END stimuli may be especially prone to acquire conditioned compensatory responses, which may counteract the CS+ evoked arousal in preparation for smoke intake found in this study (see Experiment 2: Smoking stimuli from the beginning and terminal phase of cigarette consumption support the conditioning of different physiological responses).

Although physiological arousal is one major component of incentive motivation it is certainly not a reliable index of the valence of an incentive motivational state. According to incentive theories drug-associated stimuli are hypothesized to be appetitive in nature, functioning to organize the different response systems involved in the procurement and con-

sumption of drug. In line with this assumption the CS+ for smoke reward increased the activity of the zygomatic muscle, indicative of positive affect. In contrast, the activity of the corrugator muscle failed to decrease during presentation of the CS+. It is not entirely clear, why the activity of the zygomatic muscle was sensitive to the experimental contingencies whereas the activity of the corrugator muscle was not. Interestingly, in the study conducted by Geier et al. (2000) activity of the corrugator muscle did not differentiate between positive, neutral and smoking pictures and was sensitive to the presentation of negative pictures only. In a study conducted by Waters et al. (2009a) corrugator activity was also insensitive to the presentation of smoking cues. In this study an attentional bias to smoking cues was measured by a Stroop task. Interestingly, Stroop interference was positively associated with zygomatic activity however a correlation with corrugator activity was missing.

According to incentive notions of drug addiction the function of the positive affective state activated by drug stimuli is to promote reward-directed behavior finally giving rise to the consummatory response. Thus, it may be interesting for future studies to probe the motivational effect of separately trained CSs for drug on instrumental drug taking behavior. Moreover, these Pavlovian-instrumental transfer tests may be used to shed some light on the specificity of incentive processing (or the importance of goal expectancies) in the control of addictive behavior (Balleine & O'Doherty, 2010; Bolles, 1972; de Wit & Dickinson, 2009; Dickinson, 1989, 1997). As drug cues are proposed to activate an entire appetitive system one may expect them to - at least partially - invigorate behavior supported by any US related to this system (Dickinson & Dearing, 1979; Stewart et al., 1984). However, the motivational specificity of drug cues may become apparent as the behavior of interest comes closer to the consummatory response (Galarce, Crombag, & Holland, 2007). Thus, the specific motivational effects of drug cues may be particularly evident in the control of actual drug intake. Conditioned stimuli may selectively potentiate consumption of the specific US, they have been paired with previously. Moreover, one may hypothesize a close temporospatial contiguity as especially important for the acquisition of consummatory response tendencies.

In this regard, it is notable that the present study found increased activity of the orbicularis oris muscle (lip-muscle) during CS+ trials. Enhanced activity of the lip muscle most likely reflects preparation for smoking since smoke uptake from a cigarette is accomplished by drawing smoke into the mouth followed by a deep inhalation (Müller et al., 2003). In line

with this notion are results reported by Mucha et al. (1998), who showed that an experimentally produced cue for smoking actually increased overt smoking behavior. These data are further in accordance with previous studies, which revealed an effect of naturalistic smoking cues on the topography of smoking, as indexed by a shortened latency to smoke (Droungas et al., 1995; Payne et al., 1991; Surawy et al., 1985), prolonged duration of smoking (Payne et al., 1991) and enhanced number of puffs on the cigarette, respectively (Hogarth et al., 2010; Surawy et al., 1985). Finally, these results are supported by animal studies which point to the importance of Pavlovian CSs in the self-administration of drug. For example, a study by Corbit and Janak (2007) demonstrated that a separately trained Pavlovian CS+ for ethanol increased operant responding for ethanol. Furthermore, previous studies showed that nicotine conditioned stimuli crucially affect nicotine self-administration (Caggiula et al., 2002b; Goldberg et al., 1981), retard extinction of self-administration (Cohen et al., 2005; Donny et al., 1999) and reinstate nicotine seeking after completed extinction (Le Foll et al., 2012; LeSage et al., 2004; Liu, Caggiula, Palmatier, Donny, & Sved, 2008). In sum, the results of the present study are in line with notions of incentive theories that conditioned incentive stimuli evoke appetitive and consummatory responses directed to the incentive (Berridge, 2004). They may provide a fruitful basis for further research which may benefit from the application of other objective measures of motivational valence and systematic manipulations of the test-conditions.

In the present study the clear demonstration of conditioning using physiological measures stands in contrast to the lack of conditioned subjective responses. Neither self-reported craving nor subjective pleasure differentiated between the CS+ and the CS-. To explain these results one could ask if single puffs on a cigarette were indeed consciously experienced as rewarding by smokers. According to Berridge and Kringelbach (2008) reward can be divided into several psychological components and the hedonic impact of rewarding stimuli can be dissociated under certain conditions from their motivational effects. Furthermore, objective hedonic reactions ("liking", with quotation marks) - measured in the form of facial expressions – do not necessarily have to be accompanied by conscious subjective pleasure (liking, without quotation marks). The same distinction can be made in the case of wanting (Berridge & Kringelbach, 2008; Berridge & Robinson, 2003) and indeed, there are empirical data which support the assumption that emotional reactions may sometimes be too subtle to overcome the threshold of subjective experience, but still may have

an influence on behavior (Childress et al., 2008; Winkielman, Berridge, & Wilbarger, 2005). Further support for this notion comes from studies with human drug users, who showed a behavioral preference for low doses of a drug in absence of any subjective effects (Hart et al., 2001; Lamb et al., 1991). Therefore, these results might be interpreted accordingly and may point to impaired insight into the motivational processes underlying drug addiction (Goldstein et al., 2009; Moeller et al., 2010). However, such a conclusion could be challenged by studies which demonstrated convincingly, that the availability of single puffs on a cigarette increases subjective craving and pleasure in smokers (Bailey et al., 2010; Carter & Tiffany, 2001).

To account for the different results of these studies it may be important to note that in the cue availability paradigm (Bailey et al., 2010; Carter & Tiffany, 2001) the rating data are assessed in anticipation of smoke reward. In contrast, in the present study subjective responses to the CSs were assessed after the preconditioning phase and after each block of the conditioning phase. Therefore, it might have become clear to the participants that smoking was no longer available. This reduced expectancy to smoke might have the same effect as extinction learning. In line with this assumption there are reports indicating that a cognitive representation of fear can induce anxious feelings and activation of the amygdala (Phelps et al., 2001; but see Mechias, Etkin, & Kalisch, 2010). Similarly, an instructed expectancy to smoke increased cue-evoked craving (Droungas et al., 1995). Finally, Field and Duka (2001) have shown that the removal of smoke expectancy after conditioning by instruction eliminated the subjective craving response to the CS+ (for a review of the status of smoke expectancies in cue reactivity see Hogarth & Duka, 2006; Jędras, Jones, & Field, 2014). Further studies could therefore benefit from the assessment of subjective responses to the CSs during conditioning in anticipation of smoking. Moreover, the putative role of extinction can be further substantiated by demonstrating the presence of common phenomena like spontaneous recovery, reinstatement or renewal of conditioned responding, which suggest that extinction probably involves some form of inhibitory learning (Bouton, 2000; Bouton, Westbrook, Corcoran, & Maren, 2006; Kim & Jung, 2006; Myers & Davis, 2007; Shaham et al., 2003).

Finally, it is worth mentioning that the results of the present study emerged as a net effect of the differential responses elicited by the CS+ and CS- for smoke reward. Thus, excitatory and inhibitory conditioning processes can be stressed to account for the results. Alt-

hough the involvement of inhibitory learning processes was not the topic of the present experiment, this question can be fruitfully addressed by the inclusion of additional control stimuli or the application of specific tests derived from the literature on inhibitory conditioning (see below).

In sum, recent studies have demonstrated that experimentally produced cues for smoking elicit subjective craving, physiological drug-related responses and overt drug seeking behavior in humans. The present study further extends those data by including physiological measures of motivational valence and demonstrates that an experimentally produced cue for smoking elicits facial reactions, which may be indicative of appetitive and consummatory motivation. The implications of these findings are that stimulus-evoked motivational tendencies to seek out and consume a drug may at least partly play a significant role in the maintenance of addiction and relapse in the natural environment (O'Brien, Childress, Ehrman, & Robbins, 1998).

EXPERIMENT 2: SMOKING STIMULI FROM THE BEGINNING AND TERMINAL PHASE OF CIGARETTE CONSUMPTION SUPPORT THE CONDITIONING OF DIFFERENT PHYSIOLOGICAL RESPONSES

AIM OF THE SECOND EXPERIMENT

As mentioned above cue reactivity is often addressed in the framework of a simple conditioning model. Accordingly, stimuli from the smoking ritual (e.g., the sight, smell, taste of a cigarette) are seen as conditioned stimuli, putatively formed by their reliable association with the drug effect. Although stimuli from the terminal stage of cigarette consumption (END stimuli) may be optimally placed in the ritual to support conditioning (Benowitz, 1990; Jarvik et al., 2000; Mucha et al., 2008), they surprisingly lack the high cue reactivity seen for stimuli from the beginning of the intake ritual (BEGIN stimuli). These poor cue properties were revealed by subjective measures of motivation for drug (Mucha et al., 2008; Mucha et al., 1999; Stippekohl et al., 2010), physiological indices of motivational valence (Mucha et al., 2008; Mucha et al., 2006) and experimental paradigms capturing biased attentional processing (Stippekohl et al., 2012a). Moreover, in contrast to BEGIN stimuli END stimuli were shown to be unpleasant in nature (Mucha et al., 2008; Mucha et al., 1999) and accompanied by a distinct neuronal signature including deactivations in mesocorticolimbic circuits (Stippekohl et al., 2010). This further adds to the notion that the reactivity evoked by END stimuli may be unique and partially opposite to the reactivity evoked by BEGIN stimuli (Mucha et al., 2008).

Although different theoretical notions can be addressed to account for the functional significance of terminal stimuli in the control of addictive behavior (for a detailed discussion see Mucha et al., 2008), the consideration of underlying differences in the perceived availability of smoke intake or reward might be reasonable. In contrast to BEGIN stimuli, which probably signal good smoke availability, the response-pattern of END stimuli is partially consistent with their signaling poor smoke availability. This line of reasoning may provide a link into putative inhibitory effects of END stimuli. Thus, one may consider the involvement of associative processes based on the non-availability of (further) smoke intake or reward in the formation of terminal stimuli (Brody et al., 2009; Brody et al., 2006; Carter & Tiffany, 2001; Panlilio et al., 2008, 2009; Wertz & Sayette, 2001). Interestingly, BEGIN and END

stimuli were demonstrated previously to respond differently to manipulations of perceived smoke availability (Mucha et al., 2008). Moreover, one of these studies was conducted partly in analogy to a summation test used in the classic learning literature to probe putative inhibitory effects of conditioned stimuli (Papini & Bitterman, 1993; Rescorla, 1969; Williams et al., 1992). Surprisingly, END stimuli failed to fully summate with the reactivity evoked by BEGIN stimuli. Instead, craving and pleasure was reduced. Although, this would be in line with the notion that terminal stimuli may form a distinct class of drug stimuli with putative inhibitory properties, several alternative explanations may account for the results. For example, adding an END stimulus to a BEGIN stimulus may have resulted in incomplete generalization to a stimulus compound, thereby producing a decrement in response. Furthermore, decreased reactivity may have become evident as a result of stimulus averaging (Anderson, 1965). Finally, END stimuli may have drawn attention away from BEGIN stimuli. Although unlikely, given the well-known attention effects of cues and the data of Stippekohl et al. (2012a), shifts in attention are the objection most commonly raised against an interpretation of the summation test in terms of conditioned inhibition (Hearst, 1972; Papini & Bitterman, 1993; Rescorla, 1969; Savastano et al., 1999; Williams et al., 1992). Actually, the usage of the "two-test strategy" (i.e., the combined usage of both the summation and retardation test) was particularly motivated by the request to roughly control for shifts in attention underlying apparently inhibitory effects. Thus, converging test methods have to be used to fully account for the CS properties of terminal stimuli by manipulating the predictive relationship of BEGIN and END stimuli to smoke reinforcement.

Accordingly, the second experiment of this thesis was based on the principles of the retardation procedure used in the learning literature (Rescorla, 1969). BEGIN and END stimuli were contrasted in opposing functional roles of the conditioning paradigm successfully established in Experiment 1. For half of the smokers a BEGIN picture was used as CS+ and an END picture as CS-. For the other half of the participants the assignment of the pictures was reversed. The rationale of this approach was to answer the question if the position of the conditioned stimuli in the smoking ritual affects the outcome of excitatory smoke-conditioning. In particular, this study was motivated to provide evidence for retarded excitatory conditioning in case of END stimuli. Interestingly, this paradigm may also be sensitive to the presence of conditioned compensatory responses evoked by terminal stimuli as discussed above. Skin conductance responses and facial EMG of the M. zygomaticus, M. corru-

gator supercilii and M. orbicularis oris were measured again (see Experiment 1 and Bailey et al., 2010; Bradley, 2009; Carter & Tiffany, 2001; Drobes & Tiffany, 1997; Geier et al., 2000; Hogarth et al., 2003a; Lang et al., 1993; Müller et al., 2003). In addition, the stimuli were rated in terms of craving, pleasure, arousal and expectancy to smoke. Following the suggestion mentioned in the discussion of the first experiment, stimulus ratings were conducted online in anticipation of smoke intake. The hypotheses for the conditioning of a BEGIN stimulus as CS+ for smoke reward mirrored those formulated in Experiment 1. In contrast, conditioning of an END stimulus as CS+ for smoke intake was hypothesized to be delayed, i.e., retarded.

MATERIALS AND METHODS

PARTICIPANTS

One hundred smokers aged between 18 and 40 years were recruited via advertisements from the student population of the University of Würzburg. They were included into the study if they smoked regular for more than one year with an average of at least 10 cigarettes per day. Furthermore, they had to score above three points on the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991). They were required to abstain from smoking for two hours before the experiment. Participants were excluded if they reported any signs of a major psychiatric or somatic disorder, consumption of alcohol or illicit drugs before the experiment. All subjects were fully informed about the experimental procedure and gave their written consent. The study was approved by the ethical committee of the German Psychological Association (DGPs, Deutsche Gesellschaft für Psychologie). Subjects received 18 Euro or course credit for participating. In addition, they were compensated for the cigarettes, which they provided for the experiment. Seven participants had to be excluded because of too many artifacts in the physiological recordings. Therefore, the results are based on 93 subjects (48 men and 45 women). The mean age of the participants was 24.73 years (*SD* = 4.96). They had a smoking history of 8.57 years (*SD* = 5.00), 16.08 cigarettes per day (*SD* = 4.76). The average FTND-score of the sample was 4.59 (*SD* = 1.77). Participants scored 5.80 (*SD* = 1.00) on Scale 1 (intention and desire to smoke and anticipated pleasure) of the German version of the Questionnaire on Smoking Urges (QSU-G, Müller et al., 2001). The score on Scale 2 (urge to smoke and anticipated withdrawal-relief) was 2.96 (*SD* = 1.31). Participants were distributed randomly to the experimental conditions, which differed regarding the pictures used as CS+ and CS- during conditioning (BEGIN+/END- vs.

END+/BEGIN-, see below). Both groups were comparable regarding the demographic and smoking characteristics reported above (n.s.).

STIMULUS MATERIAL

Unconditioned stimulus. One or two puffs on a freshly lit cigarette were used as unconditioned stimulus. The cigarettes were placed in a box besides the monitor, together with a lighter and an ashtray (for a detailed description see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers).

Conditioned stimuli. BEGIN and END pictures were counterbalanced between subjects in their role as CS+ and CS-. In group BEGIN+/END- the BEGIN picture served as CS+ and the END picture served as CS-. The contingency was opposite for group END+/BEGIN-. The BEGIN picture depicted a hand holding a freshly lit cigarette above an ashtray. The END picture depicted a hand butting out a finished cigarette in an ashtray. Pictures (ca. 17 cm x 12.5 cm) were presented on a screen (17 inch), in a resolution of 1024 x 768 pixels (see Figure 5, not to scale).

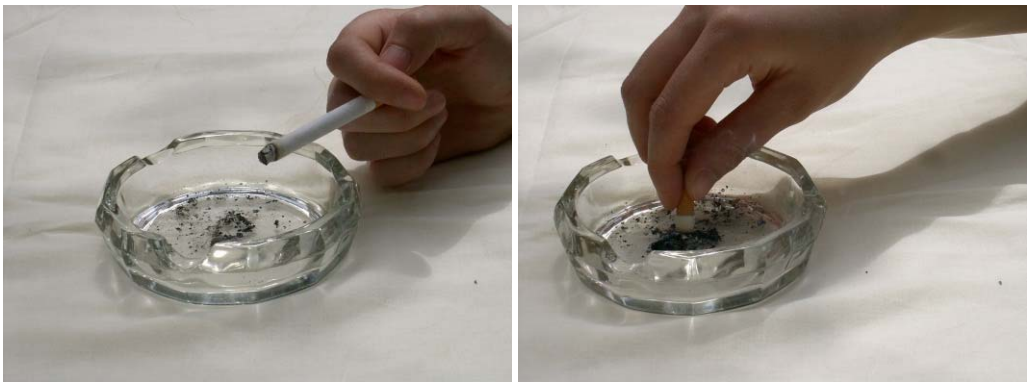

Figure 5 BEGIN and END picture counterbalanced between subjects in the role of CS+ and CS- during the conditioning phase.

PROCEDURE

The experimental protocol was adapted from the first experiment of this thesis. Overall the study took about 2.5 hours. Participants were offered some water during the experiment (after the preconditioning phase und between the two blocks of the conditioning phase). At the beginning of the study, the cigarettes of the participants were placed in a bowl. The bowl was put in a box besides the monitor, together with a lighter and an ashtray. After that, carbon monoxide (CO) levels of the participants were measured using a Bedfont Micro Smokerlyzer. Next, socio-demographic and smoking characteristics were collected and baseline craving was assessed with the QSU-G. Finally, momentary pleasure and arousal was assessed using the Self-Assessment-Manikins (SAM, Lang, 1980). Momentary craving for cigarettes and alcohol, hunger and thirst were documented using nine-point scales (not at all – high). Afterwards, participants were prepared for physiological recording. The computer-assisted part of the experiment was controlled by Presentation software (Neurobehavioral Systems, Inc.). At the beginning, subjects were familiarized with the experimental procedure by running one supervised CS+ and one CS- trial. Two neutral, abstract pictures were used for practicing (see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers). The order of picture presentation and picture – CS assignment were counterbalanced between subjects. Each trial started with the presentation of a crosshair, which was replaced by a picture after two seconds. Eight seconds after CS onset subjects rated their momentary pleasure (unpleasant-pleasant), arousal (relaxed-aroused), craving (not at all – high) and smoke expectancy (not at all – high) on nine-point scales appearing above the picture. The CS presentation continued 30 s further. In rewarded trials an instruction appeared above the CS immediately after rating and asked subjects to smoke. The participants were then required to open the box, light a fresh cigarette and take one or two puffs. Subsequently, they extinguished the cigarette and placed everything back into the box. Each CS presentation was followed by an inter-trial interval of 30 s. The actual experiment started with a preconditioning phase, in order to habituate the reactivity evoked by BEGIN and END stimuli. Each picture was presented six times without smoke reward. The picture sequence was pseudorandomized, with the restriction of no more than two repeated presentations of the same picture. At the end of the preconditioning phase, the second measurement of CO levels and subjective motivational state (SAM and nine-point scales) took place. Subsequently, the conditioning phase started, which was

divided into two blocks, each consisting of 12 CS+ and 12 CS- trials. In group BEGIN+/END-, BEGIN pictures served as CS+ and END pictures as CS-. In group END+/BEGIN- the contingency was reversed. At the end of the first conditioning block, each CS was presented again and participants were asked, if the CS was rewarded during the previous presentations (yes/no). Then CO levels and subjective state were measured the third time. After a short break, the second conditioning block started. At the end of the experiment CO and subjective state was measured the last time.

DATA RECORDING

Facial EMG was recorded with Ag/AgCl miniature electrodes (Ø = 5 mm). Electrodes were arranged in bipolar placements over the left orbicularis oris, zygomaticus major and corrugator supercilii muscle (according to Fridlund & Cacioppo, 1986). Impedance was kept below 10 kOhm. Skin conductance electrodes (Ag/AgCl, Ø = 8 mm) were filled with 0.05 molar sodium chloride paste. The two electrodes were attached to the thenar and hypothenar eminances of the non-dominant hand. Raw data were recorded using a BrainVision V-Amp 16 amplifier (Brain Products Inc.) and stored with a sampling frequency of 1000 Hz. The EMG was filtered with high- and low-pass filter settings of 28 Hz and 500 Hz, respectively. The EMG data were rectified and smoothed further, using a moving average with a time window of 150 ms.

DATA REDUCTION AND STATISTICAL ANALYSIS

For the EMG data difference scores were calculated between the average activity during the 8 s after CS presentation and the mean activity during 1 s before picture onset. Skin conductance responses were quantified as difference between the peak-value in a time frame between 1.0 s and 8 s after CS onset and the mean activity during the 1 s pre-stimulus baseline. Difference scores lower than 0.01 µS were set as zero. The logarithms of the SCRs (SCR + 1) were calculated before statistical analysis in order to normalize the distribution (Venables and Christie 1980). Data points for each CS were generated by averaging all trials of the preconditioning phase and the first and second block of the conditioning phase, respectively. The data of the preconditioning and conditioning phase were analyzed seperately. The preconditiong phase was analyzed by a Group (BEGIN+/END- vs. END+/BEGIN-) x Picture (BEGIN vs. END) split-plot ANOVA to test for differences before

conditioning. The data of the conditioning phase were subjected to a Group (BEGIN+/END- vs. END+/BEGIN-) x CS (CS+ vs. CS-) x Block (Block 1 vs. Block 2) ANOVA. Reported are the Pillai-Bartlett trace statistics of the multivariate approach. T-tests were used for follow-up comparisons. Alpha-niveau was set to $p = .05$ (two-tailed).

RESULTS

MANIPULATION CHECK

A comparison of the carbon monoxide levels (see Table 3) revealed that the participants complied with the experimental protocol and actually inhaled smoke from the cigarette during the conditioning phase, $F(3,85) = 127.76$, $p < .001$, $\eta_p^2 = .82$. CO levels were increased after the first block of conditioning compared to both the start of the experiment and the preconditioning phase, $t(92) = 15.88$, $p < .001$ vs. $t(90) = 18.87$, $p < .001$, respectively. A further increase was evident after the second conditioning block, $t(90) = 9.72$, $p < .001$.

CHANGES IN MOTIVATIONAL STATE DURING THE STUDY

There was a significant change in self-reported pleasure, $F(3,88) = 11.52$, $p < .001$, $\eta_p^2 = .28$, during the experiment (see Table 3). Pleasure slightly decreased after the preconditioning phase, $t(91) = 5.49$, $p < .001$, and remained stable till the end of the conditioning phase. Arousal ratings also changed during the study, $F(3,87) = 5.47$, $p = .02$, $\eta_p^2 = .16$. Arousal was enhanced after the first and second conditioning block compared to both the start of the experiment and the preconditioning phase, respectively, $t(90) = 2.89$, $p = .005$ vs. $t(91) = 3.82$, $p < .001$, respectively. As expected, craving for cigarettes reliable changed during the study, $F(3,89) = 119.69$, $p < .001$, $\eta_p^2 = .80$. Compared to the start of the experiment and the preconditioning phase craving for cigarettes was decreased after the first conditioning block, $t(92) = 13.97$, $p < .001$ vs. $t(92) = 15.51$, $p < .001$, and fell further after the second conditioning block, $t(92) = 4.89$, $p < .001$. Desire to eat also varied during the experiment, $F(3,89) = 14.05$, $p < .001$, $\eta_p^2 = .32$. Compared to the beginning and the preconditioning phase there was an increase after the first block of conditioning, $t(92) = 3.70$, $p < .001$ vs. $t(92) = 2.97$, $p = .004$, respectively, and a further increase after the second conditioning block, $t(92) = 4.45$, $p < .001$. The variation for desire to drink water was also appreciable, $F(3,89) = 13.03$, $p < .001$, $\eta_p^2 = .31$. Self-reported thirst first decreased after the preconditioning phase, $t(92) = 3.39$, $p = .001$, and then increased after conditioning block one, $t(92) = 6.07$, $p < .001$. Overall crav-

ing for alcohol was low, however compared to the group END+/BEGIN- (*M* = 1.35, *SD* = 0.34) the group BEGIN+/END- (*M* = 1.78, *SD* = 1.22) showed slightly enhanced craving, $F(1,91) = 5.58$, $p = .020$, $\eta_p^2 = .06$.

Table 3 Carbon monoxide levels (ppm) and ratings of pleasure, arousal, hunger, thirst and craving for cigarettes and alcohol (scale-range: 1-9) at the *start* of the experiment, *after* preconditioning and *after* the first and second block of conditioning [*M* (*SD*)].

	Start	Preconditioning	Conditioning 1	Conditioning 2
CO	9.24 (6.73)	8.78 (6.92)	17.66 (9.10)	23.46 (11.77)
Craving (Cig.)	6.22 (1.99)	6.46 (1.88)	3.13 (1.90)	2.41 (1.72)
Pleasure	6.58 (1.44)	5.69 (1.75)	5.88 (1.95)	5.73 (2.23)
Arousal	6.58 (1.70)	6.34 (1.82)	7.12 (1.52)	6.98 (1.83)
Hunger	3.57 (2.39)	3.84 (2.47)	4.27 (2.74)	4.98 (2.82)
Thirst	5.44 (1.99)	4.88 (2.18)	5.97 (2.06)	6.13 (2.23)
Craving (Alc.)	1.60 (1.11)	1.58 (1.02)	1.54 (1.07)	1.50 (0.90)

CONTINGENCY AWARENESS

Contingency awareness was defined as correct identification of both the CS+ and the CS-, respectively. 59.1% of the participants showed contingency awareness after the first and 87.1% after the second conditioning block (five participants in group BEGIN+/END- and seven participants in group END+/BEGIN-; n.s.).

RATING DATA

Craving. The ANOVA of the craving ratings during the preconditioning phase yielded a significant main effect of picture, $F(1,91) = 6.78$, $p = .011$, $\eta_p^2 = .07$. END pictures evoked less craving than BEGIN pictures. The analysis of the conditioning phase revealed significant main effects of CS, $F(1,91) = 36.50$, $p < .001$, $\eta_p^2 = .29$, and Block, $F(1,91) = 98.16$, $p < .001$, $\eta_p^2 = .52$. The CS+ elicited more craving than the CS- and craving decreased from conditioning block one to conditioning block two (see Table 4).

Pleasure. The analysis of the preconditioning phase revealed a reliable main effect of picture, $F(1,91) = 4.27$, $p = .042$, $\eta_p^2 = .05$. END pictures were rated as slightly more unpleasant

than BEGIN pictures. The ANOVA of the conditioning phase returned significant main effects of CS, $F(1,91) = 4.14$, $p = .045$, $\eta_p^2 = .05$, and Block, $F(1,91) = 20.47$, $p < .001$, $\eta_p^2 = .18$, and a reliable interaction of CS x Block, $F(1,91) = 5.29$, $p = .024$, $\eta_p^2 = .06$. The CS+ was rated as slightly more unpleasant than the CS- during the second block of conditioning, $t(92) = 2.23$, $p = .028$.

Arousal. The analysis of the preconditioning phase revealed no significant effects. The analysis of the conditioning phase revealed a significant effect of CS, $F(1,91) = 17.57$, $p < .001$, $\eta_p^2 = \eta_p^2 = .16$, and a reliable interaction of CS x Block, $F(1,91) = 14.58$, $p < .001$, $\eta_p^2 = .14$. The CS+ was rated as more arousing than the CS- during both blocks of conditioning, $t(92) = 2.44$, $p = .016$ vs. $t(92) = 4.46$, $p < .001$, respectively. The magnitude of the effect was larger in the second block.

Expectancy. The ANOVA of the preconditioning phase revealed no reliable effects. The ANOVA of the conditioning data returned a significant effect of CS, $F(1,91) = 113.48$, $p < .001$, $\eta_p^2 = .56$, and a significant interaction of CS x Block, $F(1,91) = 60.80$, $p < .001$, $\eta_p^2 = .40$. The CS+ evoked a stronger expectancy to smoke than the CS-, which was evident during both blocks of conditioning, $t(92) = 8.76$, $p < .001$ vs. $t(92) = 11.17$, $p < .001$, respectively. This difference was more pronounced during conditioning block two.

Table 4 CS evoked craving, pleasure, arousal and smoke expectancy (scale-range: 1-9) for the group BEGIN+/ END- and the group END+/BEGIN- *during* preconditioning and *during* the first and second block of conditioning [*M* (*SD*)].

		Preconditioning	Conditioning 1	Conditioning 2
Craving	BEGIN+	6.31 (2.02)	3.84 (1.95)	2.42 (2.06)
	END-	6.05 (2.03)	3.56 (1.93)	2.17 (1.92)
	END+	5.94 (2.27)	3.65 (1.83)	2.13 (1.66)
	BEGIN-	5.98 (2.19)	3.36 (1.81)	1.95 (1.43)
Pleasure	BEGIN+	5.87 (1.81)	6.04 (1.79)	5.25 (2.35)
	END-	5.80 (2.05)	6.13 (1.81)	5.71 (2.13)
	END+	5.76 (1.87)	6.55 (1.45)	5.59 (2.36)
	BEGIN-	5.98 (1.73)	6.59 (1.51)	5.82 (2.17)
Arousal	BEGIN+	3.83 (1.62)	3.26 (1.57)	3.46 (1.91)
	END-	3.84 (1.78)	3.15 (1.50)	3.01 (1.79)
	END+	3.73 (1.94)	2.96 (1.42)	3.32 (2.08)
	BEGIN-	3.69 (1.82)	2.80 (1.30)	2.78 (1.66)
Expectancy	BEGIN+	5.93 (2.04)	5.00 (2.10)	5.59 (3.32)
	END-	5.74 (2.06)	2.77 (1.55)	1.48 (1.26)
	END+	5.48 (2.41)	4.96 (2.38)	5.48 (3.38)
	BEGIN-	5.56 (2.32)	2.67 (1.70)	1.67 (1.19)

PHYSIOLOGICAL DATA

Skin conductance responses. The analysis of the preconditioning phase revealed no significant effects. The ANOVA of the conditioning phase returned a significant main effect of CS, $F(1,91) = 5.44$, $p = .022$, $\eta_p^2 = .06$, and significant interactions of CS x Block, $F(1,91) = 6.69$, $p = .011$, $\eta_p^2 = .07$, and of Group x CS, $F(1,91) = 5.25$; $p = .024$, $\eta_p^2 = .06$. The CS+ evoked stronger skin conductance responses than the CS-, particularly during the second block of conditioning, $t(92) = 2.68$, $p = .009$. Furthermore, the main effect of CS was reliable in the group BEGIN+/END- only, $t(43) = 2.67$, $p = .011$, whereas the group END+/BEGIN- showed no reliable discrimination (see Figure 6).

M. orbicularis oris. The ANOVA of the preconditioning phase revealed no significant effects. The analysis of the conditioning phase revealed a highly significant effect of CS, $F(1,91) = 6.83$, $p = .011$, $\eta_p^2 = .07$; the CS+ evoked more activity of the lip-muscle than the CS- (see Figure 7).

M. zygomaticus major. The analyses of the preconditioning and conditioning phase revealed no significant effects.

M. corrugator supercilii. The ANOVA of the preconditioning phase yielded no significant effects. The analysis of the conditioning phase returned a significant interaction of Group x Block, $F(1,91) = 8.63$, $p = .004$, $\eta_p^2 = .09$, and a reliable interaction of Group x CS x Block, $F(1,91) = 7.17$, $p = .009$, $\eta_p^2 = .07$. The group BEGIN+/END- showed a significant main effect of Block, $F(1,43) = 6.43$, $p = .015$, $\eta_p^2 = .13$, and a significant interaction CS x Block, $F(1,43) = 5.83$, $p = .020$, $\eta_p^2 = .12$. The CS+ evoked less corrugator activity than the CS- during the second block of conditioning, $t(43) = 2.08$, $p = .051$. In contrast, the corresponding ANOVA for the group END+/BEGIN- returned no reliable effects (see Figure 8).

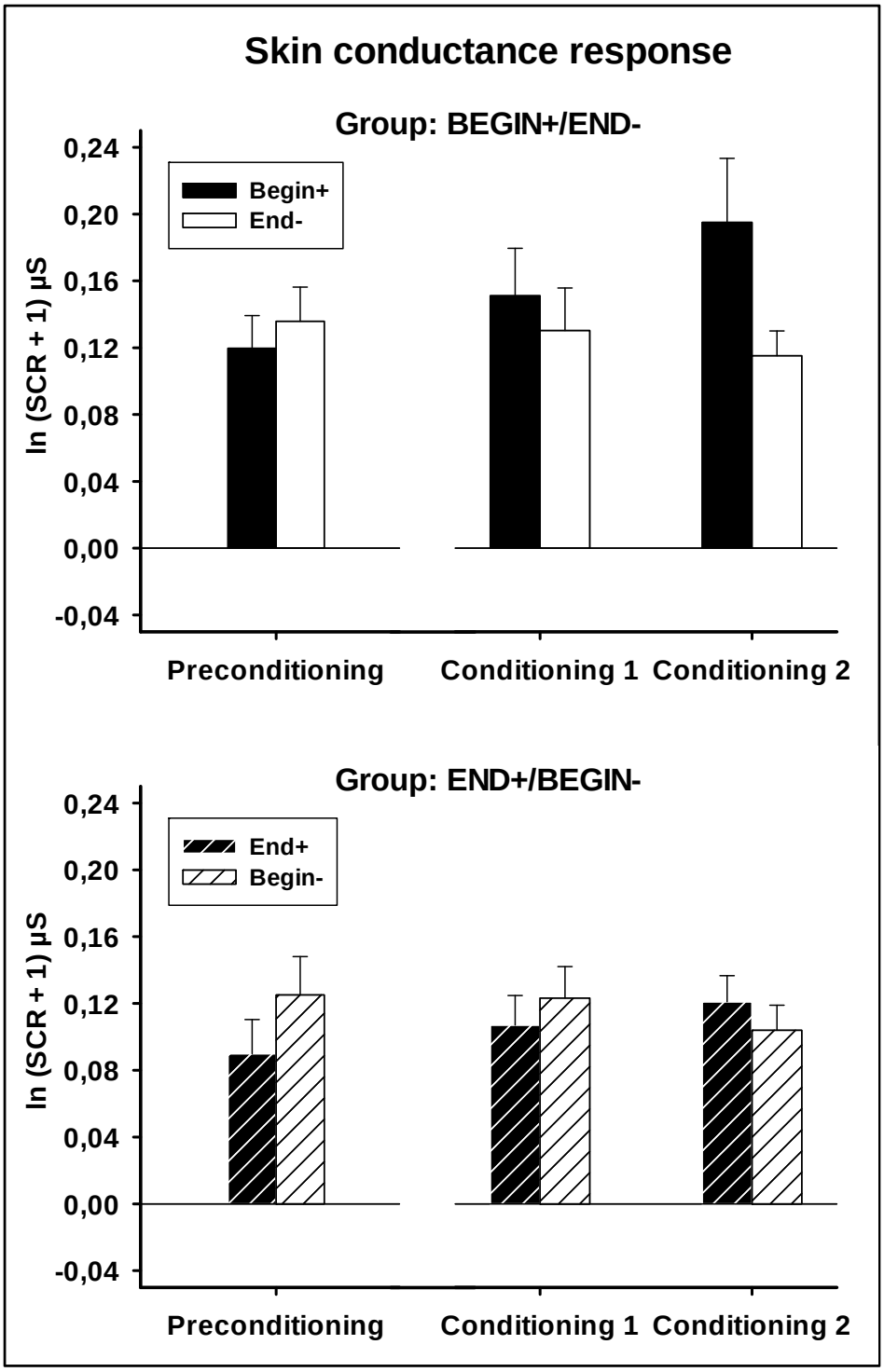

Figure 6 CS evoked skin conductance responses [ln (SCR+1) µS] during preconditioning and during the first and second block of conditioning [*M* (*SE*)]. The upper part of the figure shows the results for the group BEGIN+/END- (filled bars). The lower part of the figure shows the results for the group END+/BEGIN- (dashed bars).

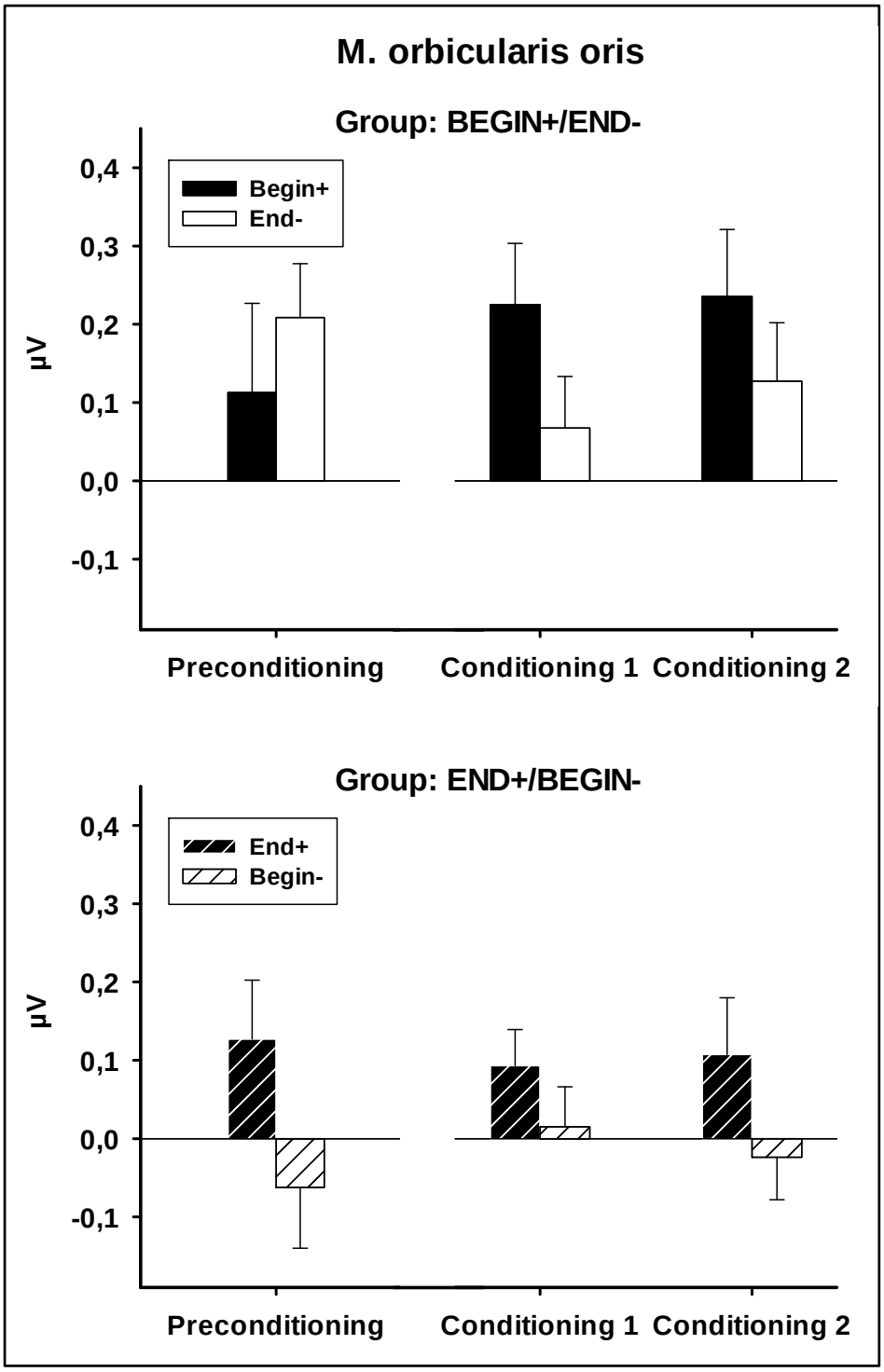

Figure 7 CS evoked activity (µV) of the M. orbicularis oris during preconditioning and during the first and second block of conditioning [*M* (*SE*)]. The upper part of the figure shows the results for the group BEGIN+/END- (filled bars). The lower part of the figure shows the results for the group END+/BEGIN- (dashed bars).

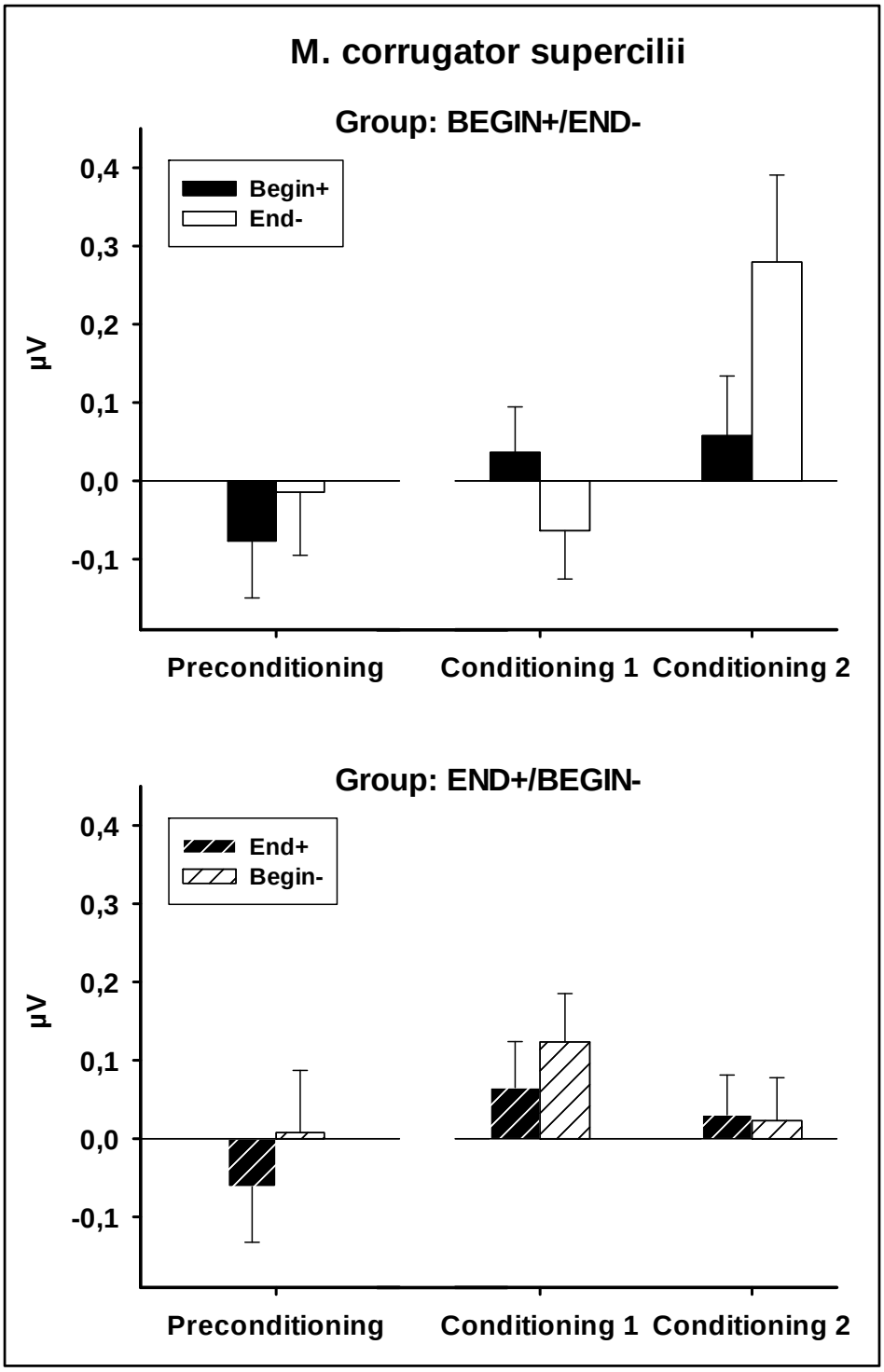

Figure 8 CS evoked activity (µV) of the M. corrugator supercilii during preconditioning and during the first and second block of conditioning [*M* (*SE*)]. The upper part of the figure shows the results for the group BEGIN+/END- (filled bars). The lower part of the figure shows the results for the group END+/BEGIN- (dashed bars).

DISCUSSION

The present study addressed the issue of apparently weak cue reactivity seen for terminal smoking stimuli. As reported previously stimuli from the terminal stage of the smoke intake ritual (END stimuli) seem to evoke unique reactivity, which may partly oppose the reactivity to BEGIN stimuli (Mucha et al., 2008; Mucha et al., 1999; Stippekohl et al., 2010). The current experiment capitalized on features of the retardation procedure used in the learning literature to probe putative inhibitory effects of conditioned stimuli (Papini & Bitterman, 1993; Rescorla, 1969; Williams et al., 1992). END stimuli were contrasted with BEGIN stimuli in opposite functional roles of a differential conditioning paradigm to investigate the development of experimentally conditioned responses.

The results clearly demonstrated conditioning of subjective and physiological responses to pictures of the smoking ritual. Importantly, the physiological measures showed a divergence between BEGIN and END stimuli during conditioning in terms of motivational valence as assessed with facial EMG of the corrugator ("frowning") muscle. Generally, activity of the corrugator muscle shows an increase with negative affect (Lang et al., 1993; Larsen et al., 2003). Accordingly, the pairing of a BEGIN stimulus with smoke intake brought about a discrimination indicative of decreased negative affect during rewarded trials. In contrast, the pairing of an END stimulus with smoke intake failed to produce a reliable discrimination. These results indicate that the motivational properties of BEGIN and END stimuli are differentially influenced by their predictive relationship to smoke intake. Furthermore, the data for the conditioning of a BEGIN stimulus are in line with incentive notions of drug addiction, arguing that drug cues elicit an appetitive motivational state, fulfilling preparatory functions like approach (Stewart et al., 1984; Wise & Bozarth, 1987). Support for this assumption comes from animal place preference conditioning (Le Foll & Goldberg, 2005, 2006; Tzschentke, 2007) and human studies measuring physiological indices of motivational valence (see Experiment 1 and Cinciripini et al., 2006; Dempsey et al., 2007; Drobes & Tiffany, 1997; Geier et al., 2000). Interestingly, the current data revealed a pronounced dissociation between subjective and objective measures of pleasure (see below), a pattern of results proposed by incentive sensitization theory (Robinson & Berridge, 1993) and seen before in detoxified alcoholics (Grüsser et al., 2002; Mucha et al., 2000; Nees et al., 2012). In direct contrast to the predictions of incentive theories, END stimuli apparently failed to acquire

positive incentive motivation as indexed by facial EMG. This resistance to positive reinforcement can be interpreted in light of previous studies (Papini & Bitterman, 1993; Rescorla, 1969; Williams et al., 1992), which provided evidence for the retarded acquisition of an excitatory conditioned response by a conditioned stimulus with putative inhibitory properties (see below).

Moreover, the skin conductance data revealed a similar divergence between BEGIN and END stimuli. The association of a BEGIN picture with smoke uptake resulted in larger skin conductance responses during rewarded trials. Besides attentional orienting increases in skin conductance are intimately connected with the arousal component of an incentive motivational state, indexing the intensity of activation of a motivational system (Lang et al., 1992; Lang & Davis, 2006). Accordingly, conditioning of a BEGIN stimulus resulted in increased salience and autonomic arousal in preparation for action (Bradley, 2009), which further highlights its motivational significance. In contrast, the pairing of an END picture failed to produce conditioning again. This is particularly striking as increases in skin conductance are probably one of the most commonly reported physiological responses in cue exposure studies (Bailey et al., 2010; Carter & Tiffany, 1999, 2001). Moreover, in the human conditioning literature it was argued cogently that differential autonomic conditioning relies heavily on the awareness of the experimental contingencies (Lovibond & Shanks, 2002, see also Hogarth & Duka, 2006 and Jędras, Jones, Field, 2014, for a discussion of the importance of drug-expectancy for stimulus control in tobacco addiction). However, in the present study most participants acquired contingency awareness and both experimental groups did not differ in terms of their explicit expectancy to smoke (see below). Accordingly, the association of an END stimulus with smoke uptake resulted in the acquisition of explicit knowledge about stimulus-reward associations without any objective indication of motivational engagement. To account for these results, it might be worth mentioning that in previous studies with neutral picture stimuli conditioned changes in skin conductance were readily observed (see Experiment 1 and Hogarth et al., 2003a). This weakens the notion that the resistance of terminal stimuli to excitatory conditioning is simply a result of being them inert or weak forms of cues. Instead, it may be suggestive of the presence of some form of reactivity opposing the acquisition of conditioned responding.

Regarding the type of mechanism involved it may be worth considering the implications of a common argument used in the animal literature to discount retarded conditioning

as reflecting a failure to appropriately attend to the conditioned stimulus. Yet, it seems unlikely that the participants simply ignored the END stimulus during rewarded trials as they showed a discrimination in terms of subjective evaluation and anticipatory motor activity. This argues against a simple attentional explanation of retarded conditioning (Rescorla, 1969). However, classic learning theories differ heavily in the emphasis of attention in conditioning (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972). Thus, the necessity to roughly control for shifts in attention as explanation of retarded conditioning of END stimuli may be dependent on theoretical prejudice. For instance, Rescorla´s original suggestions (Rescorla, 1969) were made prior to the publication of a conditioning model which disregarded the impact of learning on attentional processing. Instead, conditioned excitation and inhibition were conceptualized as symmetrical opposites on a continuum of associative strength (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972). In contrast, other well-known theories acknowledge the role of attention but make diametrically opposite predictions regarding to the alteration of attention during conditioning (Mackintosh, 1975; Pearce & Hall, 1980). For example, the conditioning model proposed by Pearce and Hall (1980) predicts a reduction in attention during learning as the predictive value of conditioned stimuli reaches asymptotic strength. In contrast, Mackintosh (1975) proposed an increase in attention to reward associated stimuli. The later prediction is mirrored by incentive motivational accounts and was probably made most "salient" in descriptions of incentive sensitization theory (Bindra, 1978; Robinson & Berridge, 1993; Stewart et al., 1984). This theory highlights the importance of associative processes for the direction of sensitized incentive motivation to the act of drug taking, thereby rendering drug-associated stimuli salient, attractive and "wanted". Thus, the ability to capture and maintain attention is hypothesized as a critical feature of drug cues. Certainly, stimulus evoked increases in skin conductance are not a biunique readout of attentional engagement. However, they are commonly considered as an important component of the orienting response and are associated with physiological arousal. Moreover, in previous smoke conditioning studies with neutral pictures conditioned skin conductance responses (see Experiment 1 and Hogarth et al., 2003a) were correlated with an attentional bias measure (Hogarth et al., 2003a). This line of reasoning emphasizes the necessity to further investigate the attentional properties of terminal stimuli. Although preliminary data point to a lack of an early attentional bias to END stimuli (Stippekohl et al., 2012a), it may be fruitful to directly address the time course of attentional processing of

terminal stimuli with high-resolving measures of resource allocation (Conzelmann et al., 2010; Field, Mogg, & Bradley, 2006; Gerdes, Alpers, & Pauli, 2008; Miskovic & Keil, 2013; Peck, Jangraw, Suzuki, Efem, & Gottlieb, 2009; Versace et al., 2011; Wieser, McTeague, & Keil, 2011). Thus, from an incentive motivational perspective it seems imperative to understand, why a stimulus clearly associated with smoking and the drug effect resists to attract heightened attention under conditions of immediate smoke reinforcement.

Although these data clearly demonstrate new experimentally conditioned differences between BEGIN and END stimuli they do not necessarily imply the existence of a novel mechanism underlying the reactivity to terminal stimuli. In this regard it may be interesting to discuss the present findings in light of animal studies which used the classic retardation test to probe putative inhibitory effects of conditioned drug stimuli. For instance, a famous study on the associative mechanisms of drug tolerance revealed that a CS- explicitly unpaired with the application of morphine subsequently retarded the acquisition of analgesic tolerance in comparison to various controls (Siegel et al., 1981). Similar results were reported for the sedative effects of morphine (Fanselow & German, 1982) and the hypothermic effects of pentobarbital (Hinson & Siegel, 1986). These results suggest that drug effects may be modulated by drug stimuli in opposite directions. Thus, conditioned stimuli associated with the non-availability of drug may acquire response tendencies opposite to those of drug-predictive stimuli, which may retard the acquisition of excitatory conditioned responses. Overall, these considerations emphasize the importance to consider inhibitory conditioning processes in drug addiction, which may even impact overt drug seeking behavior (Kearns et al., 2005; Weiss et al., 2007).

Thus, in dealing with the CS properties of terminal stimuli, it might be informative to address putative differences in the predictive value of BEGIN and END stimuli. As smoke uptake from a finished cigarette is not readily accomplished, BEGIN and END stimuli may be differentially predictive for an opportunity to smoke. Thus, in contrast to BEGIN stimuli, END stimuli may signal poor smoke availability, which may provide a link into a putative inhibitory function (Wertz & Sayette, 2001). This would be in line with other data on terminal stimuli, as we noted previously that the response patterns of BEGIN and END stimuli are differentially affected by manipulations of perceived smoke availability (Mucha et al., 2008). Moreover, previous studies demonstrated the importance of drug availability in the modulation of cue reactivity. For instance, experimental manipulations of the availability to smoke

resulted in decreased cue-evoked skin conductance responses when smoking was unavailable (Bailey et al., 2010; Carter & Tiffany, 2001). Furthermore, imaging studies reported decreased or even annihilated neural cue reactivity when smokers were unable to smoke immediately after the study (Hayashi et al., 2013; McBride et al., 2006; Wilson et al., 2004). Similarly, the neural response pattern of END smoking stimuli might partially reflect their signaling of poor smoke availability (Stippekohl et al., 2010). Moreover, the terminal stage of the smoking ritual may support conditioning processes hypothesized to be important for the regulation of drug intake. As END stimuli are probably well associated with the peak of nicotine (Benowitz, 1990; Jarvik et al., 2000; Mucha et al., 2008), they may provide information about the level of drug in the system. This may be an important component of a stimulus control account of drug intake, based on the saturation of neuronal substrates mediating the rewarding effects of smoking (Brody et al., 2009; Brody et al., 2006; Panlilio et al., 2008, 2009). According to this hypothesis drug administration will be terminated once the drug effect has reached a certain level, which renders *further* drug intake non-rewarding (see also Mihindou et al., 2013). Thus, the contingencies inherent in each act of drug taking may set the occasion for the availability of drug reward. Terminal stimuli may fit into this stimulus control account of drug taking as they may signal a lack of reward derived from smoking. Accordingly, differences in the availability of smoke intake or reward between BEGIN and END stimuli may have to be considered to underlie the retarded conditioning of END stimuli in the present study. Yet, this may not fully account for the functional significance of terminal stimuli, which can be discussed from several theoretical perspectives (for a detailed discussion see Mucha et al., 2008).

Besides differences in detail, pharmacological adaptive theories of drug-conditioning hypothesize drug stimuli to evoke conditioned compensatory responses opposing the physiological disturbance produced by the drug (Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel, 1975, 1989). As the function of these responses is seen in the maintenance of homeostasis one would predict a close temporal overlap with the drug effect to be particularly important for this form of conditioning (Mucha et al., 1999). Thus, END stimuli may indeed be ideally placed in the ritual to support conditioning, yet the responses acquired may function to counteract the physiological arousal produced by nicotine (Clarke, 1987; Gilbert et al., 2000; Mucha et al., 1996; Niedermaier et al., 1993). In the present study, these responses may have opposed the physiological arousal in preparation for smoking, thereby retarding

the conditioning of skin conductance. As conditioned compensatory changes are often reflexively linked to negative affect in the deprived organism (Hinson & Siegel, 1982), this mechanism may also account for the retarded conditioning of facial EMG. However, evidence for compensatory response conditioning in animal studies stems largely from non-motivational measures (Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel et al., 2000). Thus, the actual relationship between conditioned compensatory somatic responses, affective changes and the motivation for drug is still poorly understood – even in case of overt withdrawal from drug (Jackson, Kota, Martin, & Damaj, 2009; Kwilasz, Harris, & Vann, 2009; Mucha, 1987; Mucha, 1997; Skjei & Markou, 2003; Villanueva, Arezo, James, & Rosecrans, 1990; Watkins, Stinus, Koob, & Markou, 2000). Thus, the anticipatory processes involved in the homeostatic regulation of the physiological disturbance produced by a given drug may not be identical to the ones giving rise to excessive drug seeking and intake.

Moreover, there is evidence that withdrawal by itself can actually suppress reward- (Barr, Fiorino, & Phillips, 1999; Barr & Phillips, 1999) and drug seeking behavior (Hutcheson et al., 2001; Stewart & Wise, 1992), at least until new learning sets in. Interestingly, human drug users may reject further drug intake early after a binge of intake (Gawin, 1991; Gawin & Kleber, 1986), which may resemble the decrease in drug seeking during early stages of withdrawal reported in rodents (Arroyo, Markou, Robbins, & Everitt, 1998; Shalev, Grimm, & Shaham, 2002). Moreover, there is preliminary evidence stemming from animal research on the incubation phenomenon that extended drug exposure may actually decrease cue-evoked reeinstatement during early withdrawal. This, antecedent decline may at least partially contribute to the time-dependent increase in cue-evoked drug seeking (i.e., incubation) seen after prolonged phases of withdrawal (Pickens et al., 2011, p. 417). In this regard, it would be interesting to speculate about the nature of a mechanism functioning to deactivate the motivational responses giving rise to the seeking and intake stage of the drug ritual[7]. In contrast to terminal stimuli, stimuli from earlier stages of the intake ritual (e.g., BEGIN stimuli) may be especially prone to evoke preparatory responses, like approach, as suggested by incentive theories (Mucha et al., 1999; Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987). Accordingly, this line of reasoning would implicate the presence of at least two separate, partially opposing processes as discussed in various forms in the literature (Berridge, 2004; Koob & Le Moal, 2008; Nader et al., 1997;

[7] Ronald F. Mucha, personal communication.

Ramsay & Woods, 2014; Schull, 1979; Vargas-Perez, Ting, Heinmiller, Sturgess, & van der Kooy, 2007).

Although these results provide convincing evidence for a conditioned divergence between BEGIN and END stimuli in terms of motivational engagement, other measures of conditioning were apparently unaffected by the depicted stage of cigarette consumption. The EMG of the lip muscle (M. orbicularis oris) revealed heightened activity in anticipation of smoke intake, which probably reflects motor preparation of the consummatory response (i.e., sucking on the cigarette, see Müller et al., 2003). These data directly replicate and extend the results of the first study of this thesis, which used artificial picture stimuli and are consistent with other studies demonstrating that naturalistic smoking stimuli are able to increase several components of smoke intake (Hogarth et al., 2010; Mucha et al., 1998; Payne et al., 1991; Surawy et al., 1985). In addition, these results are supported by animal research which emphasizes the pivotal role of conditioned stimuli in the self-administration of drug (Caggiula et al., 2002a; Cohen et al., 2005; LeSage et al., 2004). Although the current data may suggest that BEGIN and END stimuli partially overlap in their ability to condition consummatory responses, it would be necessary to further substantiate this preliminary conclusion. Thus, it might be informative to probe the influence of both stimuli on measures of free drug intake behavior, especially under conditions of extinction (Davis & Smith, 1990; Davis & Smith, 2009; Müller et al., 2003; Rose, 2006; Schupp et al., 1999).

Finally, the rating data revealed conditioned changes in craving, arousal, pleasure and expectancy to smoke. Regarding CS+ enhanced craving, the results are generally consistent with the literature as stimulus control of craving is a well-documented phenomenon (Carter & Tiffany, 1999; Hogarth & Duka, 2006). In addition, the CS+ enhanced subjective arousal and increased the expectancy to smoke, which might be interesting in light of goal-directed accounts of drug taking (Bolles, 1972; Dickinson, 1997; Hogarth & Duka, 2006; Mucha, 1991). Finally, the CS+ for smoking evoked less subjective pleasure, which was evident during the end of conditioning only. From an incentive motivational perspective one might be tempted to expect subjective pleasure as a result of conditioning, although this does not necessarily have to be the case (Bindra, 1974; Robinson & Berridge, 1993; Stewart et al., 1984; Toates, 1994). Overall, the current results revealed a distinct dissociation between subjective and objective measures of conditioning. To account for this, one may refer to various forms of dual-process theories which propose the operation of two systems in the

control of human behavior, one based on associative principles and another one based on rules and declarative knowledge about facts and values (Bechara, 2005; Berridge & Kringelbach, 2008; Strack & Deutsch, 2004). Thus, the divergence of response systems in the present study may reflect different modes of stimulus processing, with BEGIN and END stimuli differentially affecting (re-)organizational processes in the associative system. This further emphasizes the importance of physiological measures of motivational engagement for our understanding of stimulus control in drug addiction (Berridge & Kringelbach, 2008).

Considering the implications of the present experiment, it may be worth mentioning that the results stemmed from comparisons of two single picture stimuli from the beginning and terminal stage of the smoking ritual. It would be interesting for future studies to control for repeated stimulus presentation, sensory specific CS effects (Akins, 2000; Bradley, Hamby, Löw, & Lang, 2007; Timberlake & Grant, 1975) and smoking content (e.g., by including neutral stimuli). Furthermore, motivational differences between free operant intake situations and the experimentally controlled delivery of single puffs on a cigarette have to be considered (Twining et al., 2009). Thus, further research is needed to determine how the experimental manipulations of the present study generalize to the conditions under which BEGIN and END stimuli are formed in the natural environment.

In summary, the present study clearly demonstrated conditioning of several subjective and physiological drug-related responses to naturalistic smoking stimuli. The conditioning of a BEGIN stimulus induced subjective craving accompanied by facial and autonomic changes probably reflecting appetitive and consummatory aspects of the motivation to smoke. Moreover, the present results suggest that it is imperative to better understand the CS properties of END stimuli as the physiological measures revealed a conditioned divergence in terms of motivational valence and autonomic arousal. Importantly, the apparently retarded conditioning of END stimuli may be suggestive of the presence of some form of reactivity opposing the acquisition of conditioned responding. These results further add to a growing body of data on the mechanisms underlying the reactivity evoked by END stimuli, which may differ from BEGIN stimuli in terms of their predictive relationship to smoke intake or their capacity to recruit regulatory physiological systems. Overall, the present study suggest that the consideration of the temporal position of a drug stimulus in the intake ritual might further our understanding how drug-induced changes in the functioning of motivational systems are finally translated into addictive behavior.

EXPERIMENT 3: CONDITIONED INHIBITION OF SUBJECTIVE AND PHYSIOLOGICAL REWARD-DIRECTED RESPONSES AS INDICATED BY A RETARDATION TEST

AIM OF THE THIRD EXPERIMENT

As described above, the drug conditioning literature highlights the importance of excitatory conditioning processes in the formation of drug cues (see Drummond, 2001; Mucha et al., 2008). According to incentive theories these stimuli acquire control over drug-directed responses on the basis of an incentive motivational process mediating natural reward and reward-related learning (Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987). As this research is commonly well anchored in the basic learning literature, it is particularly surprising that inhibitory conditioning processes are hardly addressed. According to several theories, stimuli predictive for the non-availability of drug may acquire the capacity to oppose the responses of excitatory conditioned drug cues (Hearst, 1972; Konorski, 1967; Pavlov, 1927; Rescorla, 1969; Savastano et al., 1999). Indeed, seminal work suggests that our understanding of the mechanisms determining whether and when cue reactivity is expressed may benefit from a stronger focus on inhibitory stimulus control (Kearns et al., 2005; Mihindou et al., 2013; Siegel et al., 1981; Stewart & Vezina, 1991; Vezina & Leyton, 2009; Vila & Miranda, 1994). Moreover, recent research on the terminal stage of smoke intake emphasizes the importance to consider the presence of inhibitory mechanisms in the formation of smoking stimuli (Mucha et al., 2008; Stippekohl et al., 2010, see also Experiment 2: Smoking stimuli from the beginning and terminal phase of cigarette consumption support the conditioning of different physiological responses). As suggested above, one may deal with the problem of terminal stimuli by hypothesizing a putative inhibitory conditioning process. Thus, END stimuli may signal the non-availability of (further) smoke intake or reward and therefore may evoke responses opposite to those evoked by BEGIN stimuli (Brody et al., 2009; Brody et al., 2006; Carter & Tiffany, 2001; Panlilio et al., 2008, 2009; Wertz & Sayette, 2001). Yet, certainly more work is needed to fully evaluate the CS properties of END stimuli and a putative inhibitory function.

Ultimately, this would require a lab-based conditioning model to overcome limitations of previous studies, arising from the use of naturalistic picture stimuli, natural intake-

situations (e.g., the emergence of satiety) and preselected samples (i.e., smokers). As the smoke-conditioning protocol is limited by the amount of smoking feasible in one study, it might be useful to rely on a reinforcer for which satiety hardly develops to speed up learning. As reward conditioned stimuli are hypothesized to activate an appetitive central state, their motivational effects may be partially overlapping (Dickinson & Dearing, 1979; Konorski, 1967; Lang et al., 1992; Sescousse et al., 2013; Seymour, Singer, & Dolan, 2007; Stewart et al., 1984; Weiss, 1978; Wise & Bozarth, 1987). Accordingly, it may be fruitful to probe reward conditioned inhibition in humans to enhance our knowledge of the mechanisms underlying the reactivity of terminal stimuli and inhibitory stimulus control in drug addiction. Thus, the rationale of this experiment was to provide "proof of concept" (see, for example, Hogarth et al., 2006a; Panlilio et al., 2008; 2009, for studies nicely mirroring this approach) for an inhibitory conditioning notion of terminal stimuli. Accordingly, an instrumental conditioning paradigm was used to model BEGIN and END stimuli as discriminative S^D (predictive for the availability) and S^Δ (predictive for the non-availability) of monetary reward. Money was used as US as it is a secondary reinforcer for which satiety hardly develops. Overall, this paradigm permits to investigate core features of incentive motivation (e.g., positive affect and reward seeking) in an efficient and convenient way. Thus, the question of interest of the last study of this thesis was whether during the acquisition phase the non-rewarded S^Δ would acquire inhibitory properties, which would delay (i.e., retard) excitatory conditioning in a subsequent retardation test. The rationale underlying this approach is the following: during the acquisition phase conditioned inhibition is established to the stimulus explicitly unpaired with the US (i.e., the S^Δ). Thus, the S^Δ is assumed to acquire response tendencies opposite to the corresponding excitor (S^D). Accordingly, efforts to transform a conditioned inhibitor into an excitatory stimulus by subsequently pairing it with the US should be impeded. Thus, compared to a novel control stimulus excitatory conditioning of a conditioned inhibitory should be retarded (hence the name retardation test).

Overall, this study considerably extends previous work on inhibitory conditioning with aversive (Christianson et al., 2012; Jovanovic et al., 2005; Jovanovic et al., 2009), non-aversive (e.g., prediction tasks with "neutral" outcomes; see, for example, Melchers et al., 2006; Migo et al., 2006; Williams, 1995) and appetitive USs (He et al., 2011), by measuring conditioned changes in three affective response systems: subjective report, physiological responses and overt behavior (e.g., Lang et al., 1998; Mauss & Robinson, 2009).

The present study started with an acquisition phase[8]. One stimulus, the excitor (E^D), was paired with monetary reward (US) and was therefore assumed to acquire excitatory properties. The other stimulus (I^Δ) was explicitly unpaired with the US and was therefore assumed to acquire inhibitory properties. Subsequently, a retardation test was used to probe for reward conditioned inhibition established to I^Δ. In this test, excitatory conditioning of I^D (now rewarded) was compared to the excitatory conditioning of a neutral control stimulus (N^D). Conditioned inhibition was hypothesized to result in delayed (i.e., retarded) excitatory conditioning.

Skin conductance responses and facial EMG of the M. zygomaticus major and M. corrugator supercilii were measured during both the acquisition phase and the retardation test. Although conditioned increases in corrugator activity have been reported several times with aversive reinforcers (Diesch & Flor, 2007; Flor et al., 2002; Guthrie & Bryant, 2006; Hermann et al., 2000), only few studies measured facial EMG during appetitive conditioning with mixed results (Armel et al., 2009; Hermann et al., 2000). Thus, to further increase the sensitivity of facial EMG to capture genuine core affect, activity of the M. orbicularis oculi (producing "crow´s feet") was recorded to assess what is commonly described as Duchenne smile (Darwin, 1872, Duchenne, 1862/1990; Ekman et al., 1990). An authentic smile is known to include both activation of the zygomatic and orbicularis oculi muscle. As instrumental conditioning was used to establish a behaviorally defined motivational baseline, response rates were recorded as an index of reward seeking. Stimulus ratings of pleasure, arousal and reward expectancy were assessed three times during the experiment: before the acquisition phase, after the acquisition phase and after the retardation test. Conditioned inhibition acquired by I^Δ during the acquisition phase was hypothesized to delay the excitatory conditioning of I^D in comparison to N^D in the subsequent retardation test. Furthermore, compared to the neutral stimulus, I^Δ was assumed to evoke subjective responses opposite to E^D at the end of the acquisition phase and after the retardation test.

[8] To summarize the experimental protocol: For the sake of convenience the stimuli used in this experiment are referred to as E for "excitatory", I for "inhibitory" and N for "neutral". These labels are retained during the different phases of the experiment. During the acquisition phase E is rewarded (E^D/I^Δ). During the retardation test both stimuli, I and N, are rewarded (N^D/I^D). For reasons of clarification the operating reinforcement contingencies are sometimes made explicit by superscript.

MATERIALS AND METHODS

PARTICIPANTS

63 participants (15 male/48 female) with an average age of 21.78 years (*SD* = 2.75) were recruited for the study, which was conducted according to the ethical standards of the fifth revision of the Declaration of Helsinki. The participants were recruited via advertisements from the student population of the University of Würzburg. Inclusion criteria were the following: aged between 18 and 40 years, German as native language, self-reported mental and physical health, no self-reported consumption of alcohol or illegal drugs before the experiment. The study lasted about 2.25 hours. Participants received either 14 Euro or course credits for their participation. In addition they received the monetary reward earned during the experiment (max. 7.2 Euro).

STIMULUS MATERIAL

Questionnaires. Motivational changes during the study were assessed using the Self-Assessment-Manikins (SAM, Lang, 1980) and nine-point-scales (see Table 5). The Self-Assessment-Manikins are stylized graphic figures depicting different values of emotional reactions on the dimensions of pleasure and arousal, respectively. Shifts in momentary desire to smoke, eat, drink water or alcohol (not at all - high) were measured using nine-point scales (see Mucha et al., 1999). Subjective state was measured three times: prior to conditioning, after the acquisition phase and after the retardation test (see below).

Unconditioned stimulus. The unconditioned stimulus (US) was a monetary reward of 10 Cent. During the study, monetary gain was signaled by the ringing of a cash register (1 s duration, 64.5 dB), played over headphones.

Conditioned stimuli. Yellow colored geometrical figures (a circle, a square and a triangle; 9 x 9 cm; see Figure 9, not to scale) were used as discriminative stimuli (see Andreatta et al., 2010). The stimuli were presented on a black background in the center of a 19 inch monitor (1280 x 1024 pixel) in front of the subjects (viewing distance approximately 70 cm). The stimuli were counterbalanced between subjects.

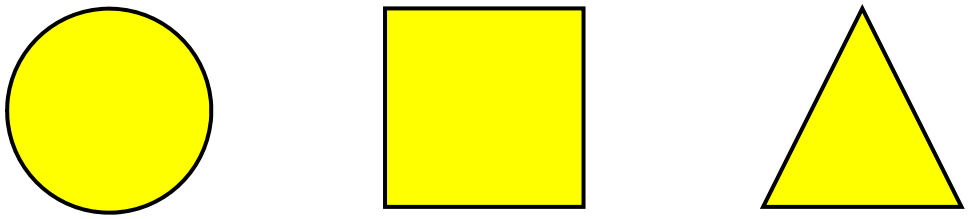

Figure 9 Stimuli counterbalanced between subjects in the role of the conditioned excitor (E), conditioned inhibitor (I) and neutral stimulus (N).

Monetary reward task. Participants were informed that they could earn money by pressing a button during a specific time interval marked by two auditory signals during stimulus presentation (i.e., the instrumental response phase). Each trial started with the presentation of the conditioned stimulus (see Figure 10). Eight seconds after stimulus onset the beginning of the instrumental response phase was marked by an auditory go-signal (20 ms white noise; 68 dB). During the following 5 s participants were allowed to press a bluely labeled response button on the keyboard. The end of the instrumental response phase was marked by an auditory stop-signal (20 ms white noise; 68 dB). The number of button presses was recorded by the computer. In rewarded trials participants were required to fulfill a response criterion of five button presses (fixed ratio schedule; FR 5) to earn a monetary reward. Three seconds after the stop-signal the US was presented. US and CS presentation were terminated conjointly. Thus, the visual stimulus was presented on screen for a total of 17 s. The next trial started after a mean inter-trial-interval of 21 seconds (16.5 – 25.5 s).

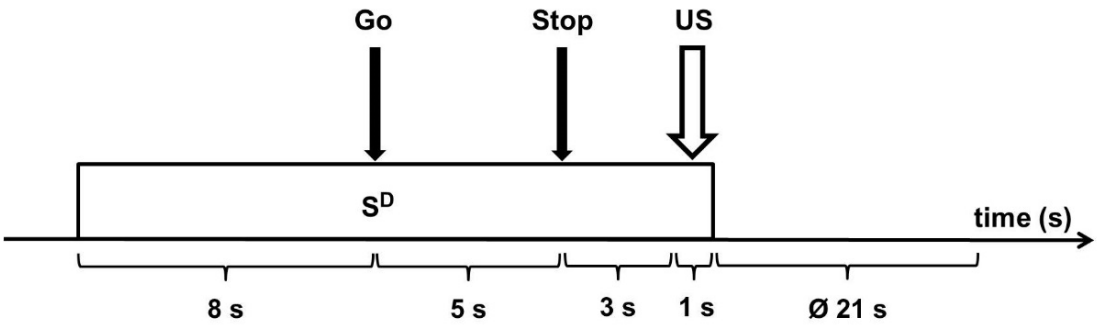

Figure 10 Scheme of the monetary reward task. Eight seconds after stimulus onset, an auditory go-signal marked the beginning of the response phase (FR 5). The end of the response phase was marked 5 s later by an auditory stop-signal. During rewarded trials (S^D) the US was presented after three seconds and terminated with stimulus presentation. The next trial started after an inter-trial interval of 21 s on average.

Experimental design. The experiment comprised two phases. During the *acquisition* phase a discriminative conditioning paradigm was used to establish two stimuli as excitatory (E^D) and inhibitory (I^Δ) reward conditioned stimuli. E^D always set the occasion for monetary reward. In contrast, I^Δ was explicitly not rewarded. The following *retardation* test was conducted to probe the inhibitory properties of I by revealing evidence for retarded excitatory conditioning. Thus, during the retardation test I^D now set the occasion for monetary reward. The acquisition of excitatory responses by I^D was compared to the excitatory conditioning of a neutral control stimulus (N^D). Each phase consisted of 24 stimulus presentations, subdivided into two blocks, in which each stimulus was presented 12 times. The sequence of the trials was pseudorandomized, with the constriction of no more than two consecutive trials of the same stimulus. Stimulus ratings were assessed prior to conditioning and after the acquisition phase and retardation test (see below).

PROCEDURE

After arrival at the laboratory, participants gave their written informed consent and completed a socio-demographic questionnaire. Subsequently, motivational state of the subjects was assessed using the SAM and nine-point scales described above. After application of the electrodes, subjects were comfortably seated in front of the computer screen and the computer-assisted part of the experiment was started. Presentation software (Neurobehavioral Systems, Inc.) was used for stimulus presentation and response registration. Instructions on the screen informed the participants about the task. Next, a practice trial of the monetary reward task was run, with a figure not further used during the experiment. Prior to conditioning the three stimuli were rated on scales appearing on the screen in terms of pleasure (unpleasant-pleasant, 1-9), arousal (relaxed-aroused, 1-9) and reward expectancy (0 – 100 percent). The sequence of stimulus presentations was counterbalanced between subjects. Next, the *acquisition* phase was run. During the acquisition phase (and the retardation test) the picture sequence was pseudorandomized, with the restriction of no more than two repeated presentations of the same picture. The acquisition phase ended with the ratings of the three visual stimuli. After the second assessment of subjective motivational state, the *retardation* test was conducted. Finally, the three stimuli were rated again and subjective motivational state was assessed for the last time. The subjects were compensated for their participation and received the money earned during the study.

DATA RECORDING

Facial EMG of the M. zygomaticus major, M. orbicularis oculi and M. corrugator supercilii was recorded from the left side of the face using a V-Amp 16 amplifier (Brain Products Inc.). Ag/AgCl miniature electrodes (Ø = 5 mm) were placed in bipolar arrangements according to guidelines provided by Fridlund and Cacioppo (1986). Impedance was kept below 10 kOhm. Skin conductance was recorded using a constant voltage (0.5 V) applied to two electrodes (Ø = 8 mm) filled with 0.05 molar sodium chloride paste. The electrodes were placed on the thenar and hypothenar eminences of the non-dominant hand. The physiological data were sampled and stored with 1000 Hz.

DATA REDUCTION AND STATISTICAL ANALYSIS

The EMG data were filtered with a high- and low-pass filter set to 28 Hz and 500 Hz, respectively. The data were rectified and smoothed with an moving average filter with a time window of 150 ms. For the facial EMG, difference scores were calculated by subtracting the average activity during a 1 second pre-stimulus baseline from the mean activity during 8 seconds after stimulus onset. Skin conductance responses (SCRs) were scored as the highest increase between 1 and 8 seconds after stimulus onset compared to a pre-stimulus baseline of 1 second. SCRs below 0.01 µS were set to zero. The SCR data were logarithmized to normalize the distribution (Venables & Christie, 1980). The behavioral data of the instrumental response phase were expressed as response rate (hits/sec). Mean responses during each condition were calculated for each block of the acquisition and retardation phase and exported for statistical analysis. The physiological and response data were analyzed separately for each conditioning phase with 2 x 2 (Stimulus x Block) repeated measures ANOVAs. Thus, the data of the acquisition phase were subjected to a Stimulus (E^D vs. I^Δ) x Block (Block 1 vs. Block 2) ANOVA. The data of the retardation phase were analyzed with a Stimulus (I^D vs. N^D) by Block (Block 1 vs. Block 2) ANOVA, respectively. T-tests were used for follow up contrasts. The subjective data were subjected to a 3 x 3 repeated measures ANOVA with Stimulus (E vs. I vs. N) and Phase (Preconditioning vs. Acquisition vs. Retardation) as factors. Reported are the Pillai-Bartlett trace statistics of the multivariate approach. Follow up comparisons between stimuli were made with ANOVAs, followed by t-tests. For the statistical comparisons alpha was set to .05 (two-tailed).

RESULTS

CHANGES IN MOTIVATIONAL STATE DURING THE STUDY

Self-reported pleasure significantly changed during the study, $F(2,57) = 17.10$, $p < .001$, $\eta_p^2 = .38$ (see Table 5). Subjective pleasure was decreased after the *acquisition* phase compared to both preconditioning $t(60) = 5.50$, $p < .001$, and after the *retardation* test, $t(58) = 3.57$, $p = .001$, respectively. The variation in arousal was also appreciable, $F(2,57) = 5.38$, $p < .001$, $\eta_p^2 = .16$. Self-reported arousal was increased after the *acquisition* phase, $t(60) = 2.24$, $p = .029$. A further increase was evident after the *retardation* phase, $t(58) = 2.06$, $p = .044$. Desire to eat also changed during the study, $F(2,58) = 9.25$, $p < .001$, $\eta_p^2 = .24$. After the *retardation* test desire to eat was enhanced, compared to both before preconditioning, $t(60) = 4.19$, $p < .001$, and after *acquisition*, $t(60) = 3.31$, $p = .002$, respectively. Further, there was a significant change in desire to drink water, $F(2,58) = 4.22$, $p = .020$, $\eta_p^2 = .13$. At the beginning of the experiment desire to drink was less than after both the *acquisition* phase, $t(60) = 1.98$, $p = .053$, and *retardation* test, $t(60) = 2.98$, $p = .004$. Desire to smoke and desire to drink alcohol didn't change.

Table 5 Ratings of pleasure, arousal, hunger, thirst and craving for cigarettes and alcohol (scale-range: 1-9) *before* conditioning and *after* the acquisition and retardation phase, respectively [*M* (*SD*)].

	Preconditioning	**Acquisition**	**Retardation**
Craving (Cig.)	1.19 (0.41)	1.19 (0.46)	1.32 (1.11)
Pleasure	7.15 (1.07)	6.16 (1.42)	6.93 (1.82)
Arousal	6.57 (1.54)	7.14 (1.82)	7.50 (1.81)
Hunger	3.37 (2.17)	3.63 (2.51)	4.30 (2.60)
Thirst	4.55 (1.96)	5.09 (2.37)	5.24 (2.18)
Craving (Alc.)	1.19 (0.34)	1.15 (0.28)	1.23 (0.64)

RATING DATA

Stimulus ratings are reported in Table 6.

Table 6 Ratings of pleasure, arousal (scale range: 1-9) and reward expectancy (scale range: 0 – 100) in response to the excitatory (E), neutral (N) and inhibitory stimulus (I) *before* conditioning and *after* the acquisition (E^D/I^Δ) and the retardation phase (N^D/I^D), respectively [*M* (*SD*)].

		Preconditioning	**Acquisition**	**Retardation**
Pleasure	E	6.24 (1.71)	6.82 (1.88)	6.37 (1.70)
	N	6.37 (1.73)	6.03 (1.80)	6.76 (1.87)
	I	6.16 (1.71)	4.97 (2.05)	6.30 (1.86)
Arousal	E	3.48 (1.73)	3.35 (2.07)	2.79 (1.89)
	N	3.44 (1.75)	2.49 (1.64)	2.87 (1.85)
	I	3.46 (1.79)	3.29 (1.90)	3.11 (1.94)
Expectancy	E	52.08 (30.71)	89.49 (20.40)	51.68 (40.50)
	N	48.95 (29.60)	40.63 (30.08)	94.25 (18.84)
	I	50.08 (2.00)	13.73 (28.75)	86.13 (23.31)

Pleasure. The overall ANOVA revealed significant main effects of Stimulus, $F(2,61) = 9.56$, $p < .001$, $\eta_p^2 = .24$, Phase, $F(2,61) = 7.18$, $p = .002$, $\eta_p^2 = .19$, and a significant interaction of Stimulus x Phase, $F(4,59) = 5.83$, $p = .001$, $\eta_p^2 = .28$. The ANOVA of the preconditioning data revealed no significant differences. After the *acquisition* phase the stimulus effect was reliable, $F(2,61) = 14.03$, $p < .001$, $\eta_p^2 = .32$. As expected, the excitatory conditioned stimulus E^D evoked more pleasure than the neutral control stimulus N, $t(62) = 3.13$, $p = .003$, indicative of successful appetitive conditioning. Notably, the conditioned inhibitor I^Δ evoked less pleasure than N, $t(62) = 4.42$, $p < .001$. This conditioned change in opposite direction is in accordance with an inhibitory conditioning notion. After the *retardation* test, the stimulus main effect was still significant, $F(2,61) = 4.91$, $p = .011$, $\eta_p^2 = .14$. The putative inhibitor I^D evoked less pleasure than the neutral control stimulus, $t(62) = 3.00$, $p = .004$, suggesting delayed (i.e., retarded) excitatory appetitive conditioning.

Arousal. The overall ANOVA of the arousal data revealed a significant main effect of Stimulus, $F(2,61) = 4.12$, $p = .021$, $\eta_p^2 = .12$, and a reliable interaction of Stimulus x Phase, $F(4,59) = 2.88$, $p = .030$, $\eta_p^2 = .16$. The ANOVA of the preconditioning data revealed no reliable effect. After the *acquisition* phase, the effect of Stimulus was highly reliable, $F(2,61) = 6.52$, $p = .003$, $\eta_p^2 = .18$. Both, the conditioned excitor E^D, $t(62) = 3.27$, $p = .002$, and the conditioned inhibitor I^Δ, $t(62) = 2.85$, $p = .006$, elicited higher arousal than the neutral control stimulus N, respectively. The ANOVA of the arousal data after the *retardation* test revealed no significant effect.

Expectancy. The overall ANOVA revealed a significant main effects of Stimulus, $F(2,61) = 12.32$, $p < .001$, $\eta_p^2 = .29$, and Phase, $F(2,61) = 63.42$, $p < .001$, $\eta_p^2 = .68$, and a significant interaction of Stimulus x Phase, $F(4,59) = 68.80$, $p < .001$, $\eta_p^2 = .82$. The ANOVA of the preconditioning data returned no significant effect. After the *acquisition* phase, the corresponding ANOVA revealed successful discriminative conditioning, $F(2,61) = 131.15$, $p < .001$, $\eta_p^2 = .81$. Compared to the neutral control stimulus N, reward expectancy was increased in case of the conditioned excitor E^D, $t(62) = 11.41$, $p < .001$, and decreased in case of the conditioned inhibitor I^Δ, $t(62) = 4.92$, $p < .001$. Thus, as expected, conditioning affected the expectancy data in opposite ways. After the *retardation* phase, the variation of the reward expectancy data was still appreciable, $F(2,61) = 61.37$, $p < .001$, $\eta_p^2 = .67$. Compared to the neutral control stimulus (N^D) reward expectancy was still decreased for the putative inhibitor (I^D), $t(62) = 3.86$, $p < .001$,, indicating retarded conditioning. However, compared to the excitatory stimulus of the acquisition phase (E) the conditioned inhibitor I^D evoked a higher reward expectancy, $t(62) = 5.34$, $p < .001$.

PHYSIOLOGICAL DATA

M. zygomaticus major. Neither the analysis of the *acquisition* phase nor the analysis of the *retardation* phase revealed significant effects.

M. corrugator supercilii. The analysis of the *acquisition* phase yielded a significant main effect of Stimulus, $F(1,62) = 6.83$, $p = .011$, $\eta_p^2 = .10$. Unexpectedly, the excitatory stimulus E^D evoked higher activity than the conditioned inhibitor I^Δ (see Figure 11). The ANOVA of the *retardation* test revealed no reliable effects.

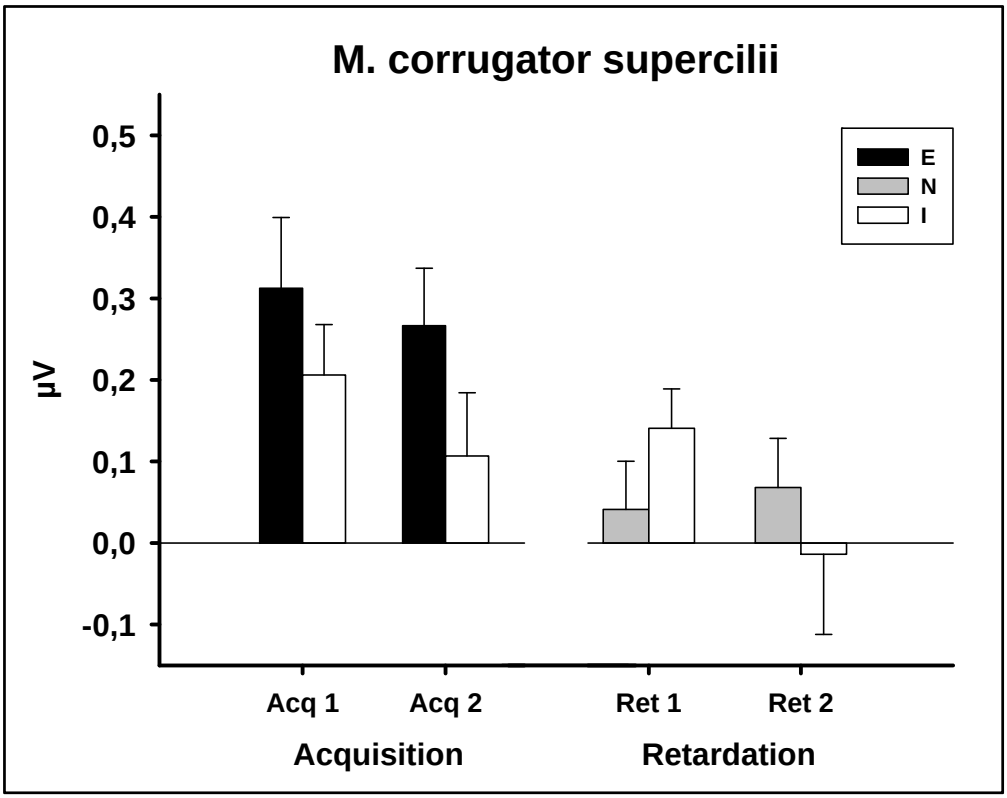

Figure 11 Stimulus evoked activity (µV) of the M. corrugator supercilii [*M* (*SE*)] during the first and second block of the acquisition (E^D/I^Δ) and retardation phase (N^D/I^D).

M. orbicularis oculi. The ANOVA of the *acquisition* phase revealed a significant main effect of Stimulus, $F(1,62) = 7.33$, $p = .009$, $\eta_p^2 = .11$. The conditioned inhibitor I^Δ evoked less muscular activity than the conditioned excitor E^D. The ANOVA of the *retardation* phase also revealed a significant main effect of Stimulus, $F(1,62) = 11.15$, $p = .001$, $\eta_p^2 = .15$. As expected, the putative inhibitor I^D evoked less activity than the neutral control stimulus N^D (see Figure 12).

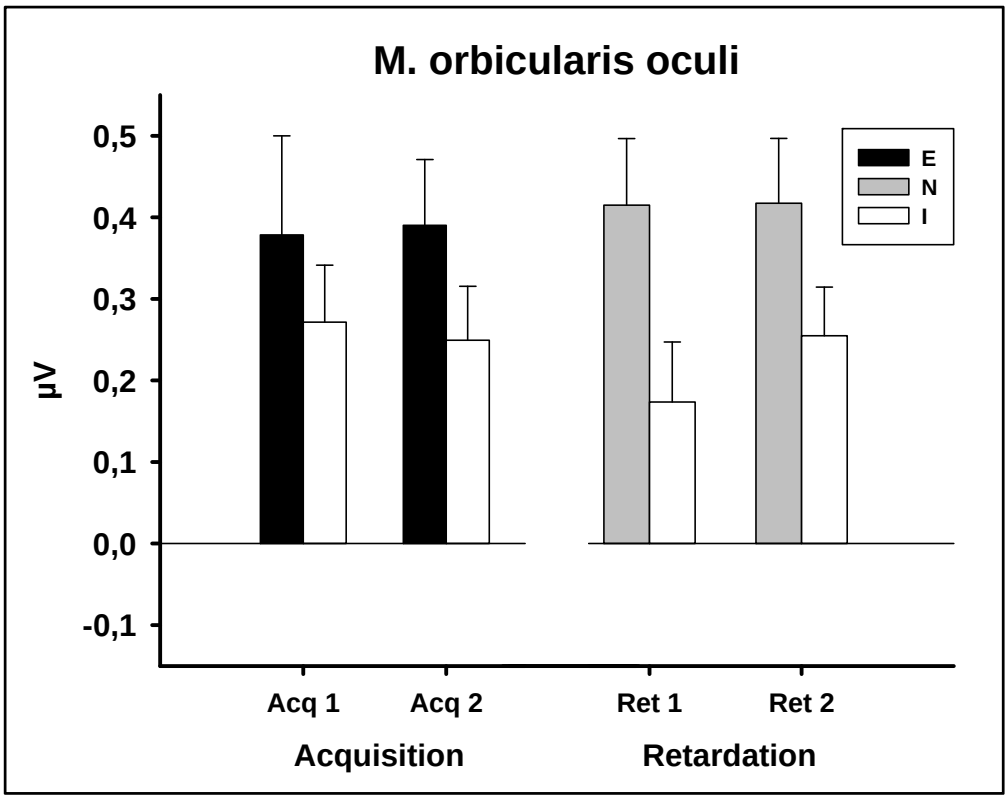

Figure 12 Stimulus evoked activity (µV) of the M. orbicularis oculi [*M* (*SE*)] during the first and second block of the acquisition (E^D/I^Δ) and retardation phase (N^D/I^D).

Skin conductance responses. The analysis revealed a significant main effect of Stimulus during the *acquisition* phase, $F(1,62) = 4.96$, $p = .030$, $\eta_p^2 = .07$. As expected, the excitatory conditioned stimulus E^D evoked larger skin conductance responses than the conditioned inhibitor I^Δ. For the *retardation* phase, the main effect of Stimulus approached significance, $F(1,62) = 3.51$, $p = .066$, $\eta_p^2 = .05$. The putative inhibitor I^D evoked somewhat lower SCRs than the neutral control N^D, which is in accordance with the hypotheses (see Figure 13).

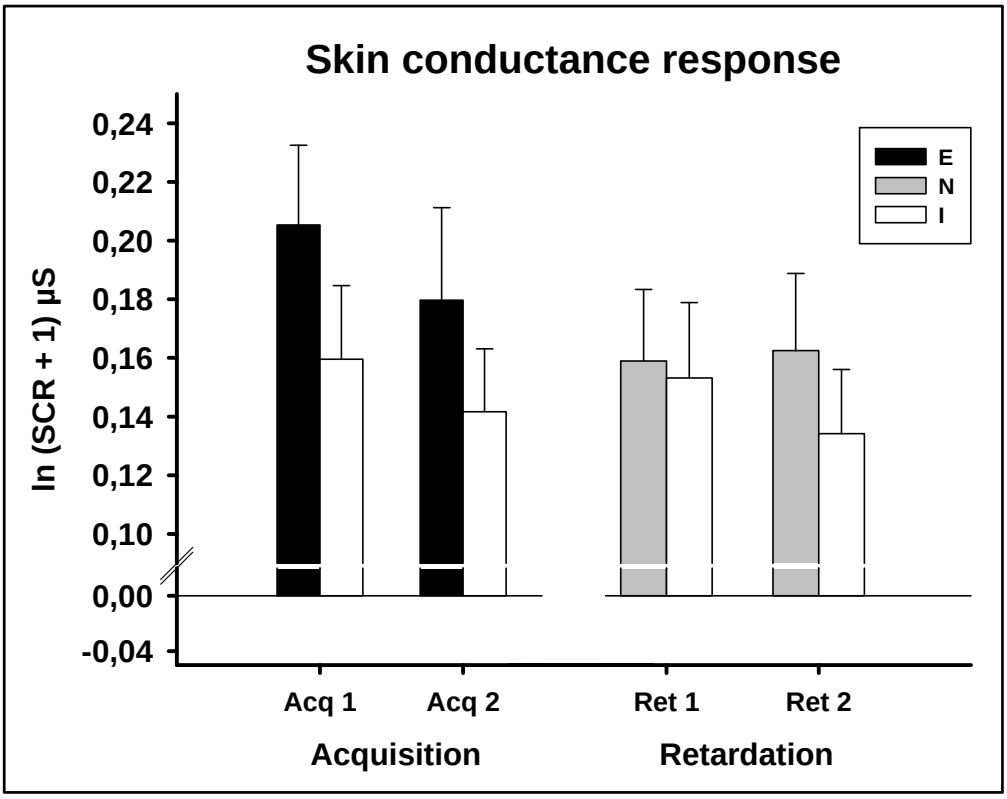

Figure 13 Skin conductance responses [ln (SCR+1) µS] during the first and second block of the acquisition (E^D/I^Δ) and retardation phase (N^D/I^D) [*M* (*SE*)].

INSTRUMENTAL RESPONSE DATA

The analysis of the behavioral data of the *acquisition* phase revealed significant main effects of Stimulus, $F(1,62) = 27.68$, $p < .001$, $\eta_p^2 = .31$, and Block, $F(1,62) = 9.95$, $p = .002$, $\eta_p^2 = .14$, and a significant interaction of Stimulus x Block, $F(1,62) = 7.05$, $p = .010$, $\eta_p^2 = .10$. The Stimulus effect was significant in both the first, $t(62) = 4.98$, $p < .001$, and second block, $t(62) = 5.07$, $p < .001$ of the acquisition phase. However, the difference was more pronounced during the second block. As expected, compared to the conditioned inhibitor I^Δ (Acq 1: $M = 2.75$, $SD = 1.77$; Acq 2: $M = 2.30$, $SD = 2.00$) the response-rate was higher during presentations of the conditioned excitor E^D (Acq 1: $M = 3.44$, $SD = 1.89$; Acq 2: $M = 3.30$, $SD = 1.83$). The ANOVA of the *retardation* test revealed no significant effects [N^D (Ret 1: $M = 3.35$, $SD = 1.77$; Ret 2: $M = 3.35$, $SD = 1.64$) and I^D (Ret 1: $M = 3.37$, $SD = 1.79$; Ret 2: $M = 3.30$, $SD = 1.67$)].

DISCUSSION

The present study investigated reward conditioned inhibition of subjective, physiological and behavioral responses to further our understanding of both terminal stimuli and inhibitory stimulus control in drug addiction and human incentive motivation. Thus, BEGIN and END stimuli were emulated as discriminative E^D and I^Δ predictive for the availability and non-availability of monetary reward, respectively. Importantly, a retardation test was used to probe conditioned inhibition acquired by the non-rewarded stimulus I^Δ of the acquisition phase (Hearst, 1972; Konorski, 1948; Pavlov, 1927; Rescorla, 1969; Savastano et al., 1999). This study demonstrated conditioned changes in multiple measures of reward processing. Moreover, this research revealed evidence in line with the notion that the association of stimuli with the non-availability of reward may give rise to conditioned inhibition in humans.

Overall, the data of the acquisition phase clearly demonstrated excitatory conditioning of the reward-paired E^D. In accordance with incentive theories (Bindra, 1974; Stewart et al., 1984) and previous studies on human evaluative conditioning (De Houwer, Thomas, & Baeyens, 2001; Hofmann et al., 2010), E^D increased subjective pleasure compared to both, the putative inhibitor I^Δ and the neutral control stimulus N. Moreover, the inhibitory conditioned stimulus I^Δ was rated as more negative than the neutral control stimulus N. Accordingly, I^Δ evoked affective responses opposite to the conditioned excitor E^D. A similar pattern of results emerged for the reward expectancy data. In line with the hypotheses, reward expectancy was decreased in case of the conditioned inhibitor I^Δ and increased in case of the conditioned excitor E^D. Importantly, the inhibitory properties of I^Δ were further substantiated by a subsequent retardation test. In comparison to the neutral control stimulus N^D, the putative inhibitor I^D delayed excitatory conditioning of subjective pleasure and reward expectancy. Thus, at the end of the retardation test I^D still evoked less pleasure and reward expectancy as N^D. These data nicely extend those of previous studies, showing that the combination of a conditioned inhibitor of shock with a transfer excitor in a summation test reduced the expectancy to obtain shock (Jovanovic et al., 2005; Neumann et al., 1997). Moreover, these results support and critically extend previous work on reward conditioned inhibition, which was limited to the assessment of mere outcome expectancies (He et al., 2011). This is especially important as conditioned emotional responses and (cognitive) expectancies were suggested previously to be partially dissociable (but see also Dawson,

Rissling, Schell, & Wilcox, 2007; Hammerl & Fulcher, 2005), to be based on different mechanisms (De Houwer et al., 2001; Hamm & Weike, 2005; Hofmann et al., 2010; Öhman & Mineka, 2001) and to be differentially involved in the control of conditioned responding (Dickinson, 1997; Hamm & Vaitl, 1996; Hogarth & Duka, 2006; Jovanovic et al., 2006; Lovibond & Shanks, 2002; Stewart et al., 1984).

Although the valence and expectancy data of the present study are apparently in line with symmetrical conceptualizations of conditioned excitation and inhibition on a continuum of associative strength (Rescorla & Wagner, 1972), the arousal data are not. At the end of the acquisition phase both conditioned stimuli (E^D and I^Δ) were rated as more arousing than the neutral control stimulus. To account for this, one may suggest that the arousing effects of the excitatory conditioned stimulus E^D generalized to the conditioned inhibitor I^Δ. However, it may be worth considering the implications of motivational theories emphasizing the reciprocal interaction of appetitive and aversive motivational systems (Dickinson & Dearing, 1979; Dickinson & Pearce, 1977; Konorski, 1967; Lang et al., 1992; Lang & Davis, 2006; Weiss, 1978). Thus, stimuli inhibiting the appetitive system mediating reward were hypothesized to activate the aversive system. Accordingly, conditioned excitors and inhibitors of opposite incentive classes may be treated as functionally equivalent (for example, regarding arousal). In contrast to motivational valence, which may be related to the activation of the respective system, indicating a disposition to act (Lang et al., 1990; Lang & Davis, 2006), subjective arousal may reflect the intensity of resource mobilization. Thus, the reward conditioned inhibitor may have activated and energized a tendency to withdraw, mirroring reports from previous animal studies showing an avoidance response to a CS- signaling the non-availability of food (Hearst et al., 1980; Wasserman et al., 1974) - at least on a subjective level. However, the increase in self-reported arousal was apparently not reflected in the skin conductance data (see below). This was expected, given the widespread use of this measure in human conditioning (e.g., Dawson et al., 2007; Hamm & Vaitl, 1996; Weike, Schupp, & Hamm, 2008). Interestingly, a similar divergence between subjective and autonomic measures of arousal was recently reported for a backward conditioned CS associated with the relief from pain (Andreatta, Mühlberger, Glotzbach-Schoon, & Pauli, 2013), which may have acquired inhibitory properties (Urcelay et al., 2008). Moreover, these results are nicely reflected by those of previous research on contextual fear conditioning (Glotzbach-Schoon et al., 2013). In this study, a CXT- predictive of the non-occurrence of shock was rated as

more arousing than a control context, although the skin conductance data revealed evidence to the contrary. As sympathetic arousal is important for action preparation (Bradley, 2009) and affected by reinforcer expectancies (Hogarth & Duka, 2006; Lovibond & Shanks, 2002), these results may indicate a lack of physiological mobilization, as the reinforcer is not expected and the test conditions failed to support an alternative disposition to act (e.g., as in concurrent choice situations; see, for example, Glotzbach, Ewald, Andreatta, Pauli, & Mühlberger, 2012; Grillon, Baas, Cornwell, & Johnson, 2006). Thus, a restricted symmetrical focus on single responses may not always be appropriate to deal with the outcome of inhibitory conditioning, as learning may engage entire motivational systems (Dickinson & Dearing, 1979; Dickinson & Pearce, 1977; Konorski, 1967; Lang et al., 1992; Lang & Davis, 2006; Silva et al., 1998; Timberlake, 2001; Tinsley et al., 2002; Weiss, 1978). In sum, the analyses of the subjective data revealed that two core components of incentive (Bindra, 1974; Stewart et al., 1984) and expectancy based models (Bolles, 1972; Dickinson, 1989, 1997), i.e., subjective pleasure and reward expectancy, showed changes in accordance with an inhibitory conditioning notion.

This view is further supported by the physiological data as the inhibitory conditioned stimulus I showed a resistance to excitatory conditioning of skin conductance and facial EMG during the retardation test (I^D/N^D). Regarding skin conductance, the data of the acquisition phase confirm the results of previous studies with aversive (Delgado, Labouliere, & Phelps, 2006; Glotzbach-Schoon et al., 2013; Weike et al., 2005), non-aversive (Hamm & Vaitl, 1996; Weike et al., 2008) and appetitive USs (Dawson et al., 2007), including monetary reward (Delgado, Gillis, & Phelps, 2008; Diaconescu et al., 2011). As expected, the conditioned excitor E^D evoked stronger skin-conductance responses than the conditioned inhibitor I^Δ, probably indicative of autonomic orienting in preparation for action (Bradley, 2009). Importantly, during the retardation test the conditioned inhibitor I^D evoked lower skin conductance responses than the neutral control stimulus N^D, indicating delayed excitatory conditioning. Moreover, these data nicely mirror the results of a previous shock conditioning study conducted by Neumann et al. (1997). These authors were probably the first who revealed evidence for conditioned inhibition of skin conductance in a summation test with a test excitor (but see also Wilkinson, Lovibond, Siddle, & Bond, 1989). Although the present results are in accordance with the hypotheses, the analysis of the skin conductance data slightly missed the criterion of significance. However, the EMG data of the M. orbicularis

oculi further substantiate the notion that I has acquired inhibitory properties as indicated by a resistance to excitatory conditioning. Moreover, several alternative explanations are unlikely to account for these results. First, the present experiment relied on a simple discriminative conditioning protocol and a retardation test to avoid problems reported in previous studies arising from configural learning, second-order conditioning, generalization decrement or external inhibition (Falls & Davis, 1997; Grillon & Ameli, 2001; Neumann et al., 1997; Williams, 1995). Second, simple attentional explanations are probably also unable to account for the results of the retardation test (Rescorla, 1969), as the instrumental response data clearly indicate that the conditioned inhibitor I^D was not ignored (see below). Third, it seems unlikely that retarded conditioning was mainly driven by a novelty response to the neutral control stimulus N^D, as all stimuli were presented earlier during the rating procedure. Moreover, even in case of the skin conductance data it was shown previously that the novelty component of the skin conductance response habituates rapidly during repeated stimulus presentations (Bradley, 2009). Thus, the present results are consistent with the view that a stimulus predictive for the non-availability of reward (i.e., the I^Δ of the acquisition phase) acquired inhibitory properties which oppose the responses to the reward predictive excitor.

Although the present experiment revealed several indications of reward conditioned inhibition, the results are constrained by the absence of evidence from corrugator activity and the behavioral data. During acquisition the excitatory conditioned E^D increased activity of the corrugator and orbicularis oculi muscle, which is inconsistent with a response pattern of a genuine Duchenne smile (Darwin, 1872, Duchenne, 1862/1990; Ekman et al., 1990). Overall, increased corrugator activity is indicative of a heightened negative affective state (Bradley et al., 2001; Larsen et al., 2003), which seems to be at odds with the application of an appetitive reinforcer. However, it was suggested previously that tightening of the brows may be a response to an obstacle encountered and may express "the perception of something difficult or disagreeable, either in thought or action" (Darwin, 1872/1998). As the participants had to accomplish a fixed response criterion, on which reward presentation was contingent on EMG activity may partially reflect resource mobilization in anticipation of the effort invested in the task. Indeed, previous research revealed increased corrugator activity during the performance of effortful mental (Smith, 1989; Van Boxtel & Jessurun, 1993; Waterink & van Boxtel, 1994; but see also Silvestrini & Gendolla, 2009) and physical tasks

(de Morree & Marcora, 2010; Morree & Marcora, 2012). This may be further accompanied by squinting the eyes, which may be reflected in increased activity of the orbicularis oculi muscle (McKenzie, 1924; Rozin & Cohen, 2003). Accordingly, in the present study enhanced corrugator activity during rewarded trials may reflect the vigor involved in instrumental responding, which is also discussed as an important function of the mesocorticolimbic system (Berridge, 2007; Salamone et al., 2007; Salamone et al., 2005). Indeed, compared to the non-rewarded I^{Δ} the conditioned excitor E^{D} strongly motivated the participants to engage in instrumental reward seeking. In fact, the response rates in the present study were that high that it seems difficult to accomplish a breakpoint of instrumental responding by simply increasing the fixed-ratio criterion of the protocol (Le Foll & Goldberg, 2006; Markou et al., 1993).

Considering the lack of retarded conditioning, the most parsimonious explanation probably is that conditioned inhibition was not strongly enough established during acquisition. Indeed, there is evidence that inhibitory learning may be delayed compared to excitatory conditioning (Weike et al., 2008). Interestingly, the analysis of the instrumental response data revealed an unexpectedly high response rate during presentations of the non-rewarded I^{Δ}. Moreover, during the last trial of the acquisition phase instrumental responding still reached the fixed ratio criterion of reinforcement[9]. This would have resulted in rapid conditioning during the retardation test. However, the response rates during I^{D} and N^{D} were already enhanced during the very first test trial, which argues against a simple stimulus-response explanation of instrumental responding. To account for this, one may consider the fact that the stimulus ratings after the acquisition phase were conducted under conditions of extinction. Moreover, as the retardation phase was announced as a new part of the experiment, a switch in experimental context may have influenced the results. Thus, as it is the case in extinction (Bouton et al., 2006; Myers & Davis, 2007; Shiban, Pauli, & Mühlberger, 2013) poor generalization of inhibitory learning to the new context of the retardation test may have contributed to the lack of retarded conditioning of corrugator activity and instrumental responding.

[9] Compared to E^{D} (M = 16.03, SD = 9.82), the response rate during the last trial of the acquisition phase was lower in case of I^{Δ} (M = 10.83, SD = 11.25), but still above the fixed ratio criterion (FR = 5). During the first trials of the retardation test instrumental responding during the presentation of both stimuli N^{D} (M = 15.86, SD = 10.32) and I^{D} (M = 17.03, SD = 10.05) exceeded the criterion of reinforcement, respectively.

Finally, it may be interesting to speculate about the psychological mechanisms underlying the control of instrumental reward seeking in the present study. According to habit theories conditioned stimuli trigger instrumental responding based on a simple stimulus-response association (Belin et al., 2009; Everitt, Dickinson, & Robbins, 2001; Hogarth et al., 2010; Hull, 1943; Thorndike, 1911). In contrast, incentive theories emphasize the appetitive motivational effects of conditioned stimuli in the guidance of reward-directed behavior (Bindra, 1974; Robinson & Berridge, 1993; Stewart et al., 1984). Instead, "goal-directed" theories focus on the importance of reward expectancies and (cognitive) knowledge about the relationships between stimulus, response and outcome (Bolles, 1972; de Wit & Dickinson, 2009; Dickinson, 1997). In this regard it might be interesting that the conditioned inhibitor I decreased both conditioned pleasure and reward expectancy at the end of the acquisition and retardation phase, respectively. However, in the present study instrumental responding also seemed to be partially uncoupled from the rating data (e.g., at the end of the retardation test). Thus, it may be fruitful to further investigate the associative architecture underlying stimulus control of instrumental behavior in future studies. Test procedures derived from the animal literature can be used to probe the relative dependency of instrumental reward seeking on the general appetitive properties of conditioned stimuli or the specific expectancies they evoke. Pavlovian-instrumental transfer tests (Balleine & Killcross, 2006) lately received heightened interest in human research as they allow to probe the differential impact of specific and general motivational effects of conditioned stimuli on instrumental behavior (Bray, Rangel, Shimojo, Balleine, & O'Doherty, 2008; Hogarth, Dickinson, Wright, Kouvaraki, & Duka, 2007; Nadler, Delgado, & Delamater, 2011; Talmi, Seymour, Dayan, & Dolan, 2008). General effects of Pavlovian-instrumental transfer might be interpreted in terms of a CS evoked activation of an appetitive system, which also enhances instrumental responding for rewards different from the one the CS was previously paired with (general, affective or outcome-independent transfer). In contrast, the motivational control of the CS may be specific, which becomes apparent in the selective potentiation of operants established by the same reward (sensory-specific, specific or outcome-dependent transfer; see Bolles, 1972; de Wit & Dickinson, 2009; Dickinson, 1997). The later effect may provide support for the importance of specific goal expectancies in the control of instrumental behavior. Interestingly, a recent study by Nadler et al. (2011) not only revealed evidence for general emotive transfer effects (which argues for the importance of the affec-

tive properties of the CS), but additionally showed that a reward conditioned CS- actually decreased instrumental responding in comparison to the period prior to stimulus presentation. These results further underscore the necessity to consider the importance of inhibitory conditioning in the control of human reward-directed behavior.

Considering the implications of the present study, it is important to realize that conditioning processes are not only involved in the acquisition of "likes" and the guidance of appetitive behavior in general (Berridge & Kringelbach, 2008; De Houwer, Baeyens, & Field, 2005; Petrovich & Gallagher, 2007; Schultz, 2006, 2007), but also in the development and maintenance of various clinical disorders (Martin-Soelch et al., 2007), including obesity (Berridge, 2009; Petrovich & Gallagher, 2007; Volkow et al., 2011) and drug addiction (Robinson & Berridge, 1993; Stewart et al., 1984; Volkow & Li, 2004). Accordingly, conditioned stimuli signaling the availability of natural (e.g., food) and artificial reinforcers (e.g., addictive drugs) are discussed to motivate (over-) consumption. In contrast, the results of the present study suggest that stimuli predictive for the non-availability of reward may acquire opposite effects. Thus, sustained learning may endow conditioned stimuli or contexts with the capacity to oppose the subjective, physiological or behavioral effects of excitatory cues. Indeed, there is rich evidence from animal studies with natural reinforcers in support of this assumption (Lombas, Kearns, & Weiss, 2008a; but see also Tinsley et al., 2002; Tobler et al., 2003; Williams et al., 2008). Moreover, even reinforcers as powerful as addictive drugs can give rise to inhibitory learning, which may counteract the expression of tolerance (Siegel et al., 1981; Vila & Miranda, 1994), sensitization (Stewart & Vezina, 1991; Vezina & Leyton, 2009) and cue-evoked drug seeking (Kearns et al., 2005; Mihindou et al., 2013). Thus, further research is needed to fully evaluate the involvement of inhibitory conditioning processes in drug addiction and human incentive motivation, an approach which turned out to be useful in case of aversively motivated behavior (Andreatta et al., 2012; Andreatta et al., 2010; Jovanovic & Ressler, 2010; Lissek et al., 2005; Lohr et al., 2007; Rachman, 1984; Waters et al., 2009b). Finally, the results of the present study may be valuable for our understanding of the mechanisms involved in the formation of cues and terminal stimuli as discussed below (see General discussion).

General discussion

The present thesis deals with the problem of stimulus control in human drug addiction and incentive motivation. This topic is especially important, given that learning processes are stressed to account for the situational-specific expression of core features of addictive disorders, e.g., increased *craving* for drug and enhanced consumption. Thus, from a theoretical and clinical perspective it is necessary to extend our knowledge of the processes involved in the formation of drug *cues* and in the prevention of cue reactivity from its expression. The present thesis attempted to reach this goal by focusing on core features of conditioning and modern developments in the field of animal learning. Thus, a series of conditioning studies was run to clarify the motivational properties of smoking associated stimuli. This research revealed evidence for 1) an appetitive nature of excitatory conditioned smoking cues, 2) the dependency of this learning process on the temporal position of the conditioned stimuli in the intake ritual and 3) the acquisition of conditioned inhibition by a stimulus predictive for the non-availability of reward, as evident in retarded excitatory conditioning.

In sum, these studies made a novel contribution to the field by using physiological measures targeting preparatory and consummatory components of the motivation to smoke (Drobes & Tiffany, 1997; Müller et al., 2003), which have been neglected by previous smoke conditioning studies so far. As (drug) reward gives rise to several (psychological) processes not necessarily reflected in subjective report (Berridge & Robinson, 2003), this approach allowed to gain insight into the emotional foundation of conditioned responding on the basis of objective measures of motivational valence. This is especially important in case of addicted humans as drug reinforcers may motivate self-administration outside of conscious awareness (Childress et al., 2008; Hart et al., 2001; Lamb et al., 1991). In particular, dependent users may show impaired insight into the motivational organization of the processes controlling their behavior (Goldstein et al., 2009; Moeller et al., 2010; Mucha et al., 2000). Furthermore, physiological measures of motivational valence are relevant in light of prominent theories which differentially appreciate the importance of appetitive conditioning processes in the formation of drug cues (Everitt & Wolf, 2002; Koob & Le Moal, 2005; Robinson & Berridge, 1993; Siegel et al., 2000; Stewart et al., 1984; Tiffany, 1990). Moreover, the present research provided new, systematic information on the relationship between BEGIN and END stimuli and in particular addressed a putative inhibitory function of the lat-

er. The consideration of inhibitory learning processes critically extends the prevailing focus on excitatory conditioning in the control of conditioned responding and fits well into a recent line of research, which highlights the capacity of drug reinforcers to give rise to inhibitory learning (e.g., Kearns et al., 2005; Lombas et al., 2008b; Mihindou et al., 2013).

In contrast to the vast amount of human cue reactivity studies which are necessarily correlative in nature, the *first experiment* of this thesis (see Experiment 1: Conditioned cues for smoking elicit appetitive and consummatory responses in healthy smokers) revealed clear evidence for the conditioning of physiological responses to a previously neutral CS+ for smoke reinforcement. In line with the predictions of incentive theories (Bindra, 1974; Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987), the CS+ enhanced activity of the zygomatic muscle, indicating an appetitive response in anticipation of smoke reward. These data are remarkable, as the conditioning protocol possessed several features (e.g., "forced" smoking, high smoke intake), making this outcome less likely. Importantly, the orbicularis oris muscle showed an parallel increase in activity, which probably reflects motor activity in preparation of the consummatory response, i.e., puffing on a cigarette (Müller et al., 2003). The skin conductance data further support the view that the CS+ acquired motivational significance, as indicated by increased autonomic arousal and orienting in preparation for action (Bailey et al., 2010; Bradley, 2009; Carter & Tiffany, 2001; Hogarth et al., 2003a). In sum, these results critically extend previous work on naturalistic smoking stimuli (Carter & Tiffany, 1999), which revealed evidence for an appetitive nature of smoking cues, as indicated by the affect-modulation of the startle response (Cinciripini et al., 2006; Dempsey et al., 2007; Geier et al., 2000) and facial electromyography (Drobes & Tiffany, 1997; Geier et al., 2000). Moreover, the data of the orbicularis oris muscle suggest that a CS+ for smoke reinforcement evokes a tendency to engage in the consummatory act. These data nicely complete previous results, which showed an effect of naturalistic (Bailey et al., 2010; Surawy et al., 1985) or experimentally conditioned smoking cues (Hogarth et al., 2010; Mucha et al., 1998) on various components of overt smoking behavior (e.g., the latency to smoke, the duration of smoking and the number of puffs on a cigarette). Finally, the first study of this thesis revealed a pronounced divergence between physiological and subjective measures of conditioning, as the later failed to show a conditioned discrimination (see below). In sum, this study is the first which demonstrated smoke conditioned changes in physiological measures probably indicative of appetitive and consummatory aspects of the mo-

tivation to smoke. This is particularly important, given that cue-evoked tendencies to seek out and consume a drug have been hypothesized to essentially contribute to the maintenance of addictive behaviors and relapse in those users trying to quit (Heinz et al., 2009; Janes et al., 2010; O'Brien et al., 1998; Waters et al., 2004).

The *second experiment* of this thesis (see Experiment 2: Smoking stimuli from the beginning and terminal phase of cigarette consumption support the conditioning of different physiological responses) answered the question, whether the nature of the conditioned response depends on the temporal position of the conditioned stimuli in the smoking ritual. This approach was important for several reasons. First, it allowed to conceptually replicate the results of the first study. Thus, the conditioning of a BEGIN stimulus as CS+ for smoke reward revealed evidence for the acquisition of an appetitive physiological response, as indicated by the activity of the corrugator muscle. This was accompanied by an increased skin conductance response and activity of the orbicularis oris muscle. Differences between the two studies in terms of the specific pattern of conditioned muscular responses (zygomatic vs. corrugator) may have emerged as the result of the differential associative history of the conditioned stimuli used (i.e., neutral vs. smoking stimuli) with smoking. Interestingly, there is evidence that the upper muscles of the face are differentially innervated and less sensitive to voluntary control than those of the lower part of the face (Rinn, 1984). In line with this, the extensive association of smoking stimuli with smoke intake in the natural environment may have shifted conditioned affective responding to a basis less amenable to voluntary control. This hypothesis can be further substantiated by running an extended conditioning protocol with neutral picture stimuli or by comparing the response patterns of smokers varying in the amount of smoking. However, the important point here is that the second experiment of this thesis once again revealed clear evidence for the conditioning of appetitive and consummatory physiological responses to a CS+ predictive for smoke reward. Moreover, these results confirm the reliability of the lip EMG as sensitive index of consummatory response tendencies and suggest it as suitable for further research.

Second, this study provided new data on the CS properties of terminal smoking stimuli and in particular revealed evidence for the retarded acquisition of excitatory conditioned physiological responses. Remarkably, the conditioning of an END stimulus as CS+ for smoke reinforcement failed to produce a conditioned discrimination in terms of motivational valence and autonomic arousal, as indicated by the corrugator and skin conductance data.

Thus, these results provide additional support for the notion that terminal stimuli may be weak cues for smoking by extending the results of previous studies to conditions of immediate smoke reinforcement (Mucha et al., 2008; Mucha et al., 1999; Mucha et al., 2006; Stippekohl et al., 2012a; Stippekohl et al., 2010). More important, the retarded conditioning of END stimuli might be suggestive for an inhibitory function of terminal stimuli. As illustrated above (see above: Poor cue effects of terminal smoking stimuli), terminal stimuli may acquire conditioned responses on the basis of their predictive relationship to (further) smoke intake or reward (Brody et al., 2009; Brody et al., 2006; Panlilio et al., 2008, 2009), which may finally oppose the responses evoked by BEGIN stimuli (Mucha et al., 2008; Mucha et al., 1999; Stippekohl et al., 2010). This interpretation may be further supported by the third study of this thesis, which demonstrated that an inhibitory conditioned stimulus, previously predictive for the non-occurrence of reward, shows retarded excitatory conditioning (see below). Moreover, simple attentional explanations are probably unable to account for the retarded conditioning of END stimuli, as the rating data and the activity of the orbicularis oris muscle clearly showed that the CSs were not ignored. Furthermore, these results seem to be uncoupled from subjective reports. This is most remarkable in case of the contingency data, as the acquisition of (autonomic) conditioning is considered as highly dependent on conscious reinforcer expectancies (Lovibond & Shanks, 2002; see also Hogarth & Duka, 2006). However, most participants showed awareness of the experimental contingencies, yet failed to acquire a conditioned skin conductance and corrugator response. Thus, these results may be indicative for a restructuring of associative processes based on previous learning that smoke intake or reward is not available. Finally, these results stand in remarkable contrast to those received from the first study of this thesis with artificial conditioned stimuli, which readily showed conditioning. However, to further substantiate an inhibitory notion of terminal stimuli, it would be interesting for future studies to contrast the excitatory conditioning of END stimuli with the conditioning of neutral control stimuli. Overall, this line of reasoning emphasizes differences in the predictive value of BEGIN and END stimuli regarding to the availability of smoke intake or the reward derived from smoking (Brody et al., 2009; Brody et al., 2006; Panlilio et al., 2008, 2009) to account for the poor cue effects of terminal smoking stimuli. Importantly, this may offer a link into an inhibitory function, as stimuli signaling the non-availability of a reinforcer are commonly hypothesized to acquire response tendencies opposite to excitatory conditioned stimuli.

And indeed, previous animal studies suggest that drug reinforcers may support several forms of inhibition, which may counteract the expression of conditioned tolerance (Fanselow & German, 1982; Hinson & Siegel, 1986; Siegel et al., 1981; Vila & Miranda, 1994), sensitization (Stewart & Vezina, 1991; Vezina & Leyton, 2009) and overt drug seeking (Kearns et al., 2005; Lombas et al., 2008b; Mihindou et al., 2013; Weiss et al., 2007). Although inhibitory conditioning processes in drug addiction are hardly addressed in the human literature, several studies support the notion that cue reactivity is decreased when drug intake appears not available (Bailey et al., 2010; Carter & Tiffany, 2001; Droungas et al., 1995; McBride et al., 2006; Wertz & Sayette, 2001; Wilson, Sayette, Delgado, & Fiez, 2005). This line of research clearly suggests the availability of drug as important in the modulation of cue reactivity and adds to the notion that the CS properties of terminal stimuli may stem from their signaling the lack of an opportunity of smoke reinforcement.

In sum, the second experiment of this thesis is the first, which directly contrasted BEGIN and END stimuli in a conditioning paradigm with smoke intake as reinforcer and demonstrated a conditioned divergence in physiological measures of motivational valence and autonomic arousal. These results are particularly important as the retarded conditioning of END stimuli may provide further support for a thesis, that the CS properties of terminal stimuli may be partially inhibitory in nature. Overall, these findings support the notion that the reactivity evoked by drug stimuli is dependent on the proximity of the drug reinforcer (see below) and suggest a stronger focus on inhibitory effects of drug stimuli as valuable for our understanding of addictive behaviors. This view is further endorsed by the results of the third study of this thesis, which suggest that a stimulus predictive for the non-availability of reward acquires inhibitory properties.

Thus, the *third experiment* of this thesis (see Experiment 3: Conditioned inhibition of subjective and physiological reward-directed responses as indicated by a retardation test) relied on the retardation test used in the conditioned inhibition literature to probe putative inhibitory effects of conditioned stimuli (Rescorla, 1969; Savastano et al., 1999). This study crucially extends previous research (e.g., Christianson et al., 2012; He et al., 2011; Migo et al., 2006) by revealing evidence for reward conditioned inhibition as apparent in the retarded acquisition of excitatory conditioned subjective (pleasure and reward expectancy) and physiological (skin conductance and activity of the orbicularis oculi muscle) responses. Thus, in comparison to a neutral control stimulus the previously established I^{Δ} for the non-

availability of reward may have acquired inhibitory properties. These results are important as they suggest that a consistent association with the non-availability of reward may endow conditioned stimuli with the capacity to inhibit the reactivity of excitatory conditioned stimuli. In case of natural reinforcers such stimuli may be helpful to overcome cue-evoked temptations to eat, which are hypothesized to crucially contribute to the emergence of obesity (Berridge, 2009; Petrovich & Gallagher, 2007; Volkow et al., 2011). Moreover, the third study may be relevant for our understanding of the mechanisms involved in the formation of terminal stimuli. In particular, the results are interesting in light of the second study of this thesis, which revealed evidence for the retarded acquisition of excitatory conditioned physiological responses in case of END stimuli. Furthermore, the results of the reward conditioning paradigm crucially mirror the self-reported aversive effects of terminal stimuli, which are probably more reliable found than the pleasurable effects of cues (Mucha et al., 2008; Mucha et al., 1999; Stippekohl et al., 2010). Interestingly, the opposite predictive values of the discriminative stimuli of the reward-conditioning paradigm were nicely reflected by the expectancy data. This may be important, as the dissociation of BEGIN and END stimuli by manipulations of perceived smoke availability in the study conducted by Mucha et al. (2008) may have been mediated by the subjective expectancy to smoke. As the available data base on stimulus evoked differences in the expectancy to smoke is limited for BEGIN and END stimuli (see Experiment 2), it may be interesting for future studies to investigate the impact of experimentally manipulated expectancies to smoke on the reactivity of both stimuli (Field & Duka, 2001; Mechias et al., 2010; Phelps et al., 2001). Interestingly, the present study failed to demonstrate conditioned inhibition of instrumental reward seeking, although in general the response data nicely mirror previous results from human smoke conditioning studies (Hogarth et al., 2003a). Unfortunately, there is no direct evidence available on the impact of END stimuli on instrumental responding for drug. However, the terminal stage of smoking is (by definition) characterized by the completion of smoking. Although the results of the second experiment of this thesis may indicate that END stimuli do not differ from BEGIN stimuli in terms of their ability to acquire excitatory conditioned consummatory responses, it may be important for further studies to investigate the impact of both stimuli on (instrumental) drug seeking and consumption. Overall, the third experiment strengthens the approach to account for the CS properties of terminal stimuli by addressing their predictive relationship to smoke intake or reward. However, an interpolation of the

results has to consider methodological differences in study design, which may partially limit the generalizability of the findings. For example, running a preconditioning (extinction) phase in Experiment 2 before conditioning may have affected the sensitivity of the test-paradigm to reveal evidence for the retarded conditioning of END stimuli as reflected in self-report. Furthermore, in contrast to the reward-conditioning paradigm, both smoke conditioning studies failed to provide evidence for the acquisition of a pleasure-response by a CS+ for smoking. Although interesting, given the ongoing debate about the functional role of subjective pleasure in the control of human drug seeking (Hogarth et al., 2010; Hogarth & Duka, 2006; and see below), this result may also point to important differences between primary and secondary reinforcers (e.g., susceptibility to satiety) or Pavlovian and instrumental conditioning preparations (Kalant, 2010; Twining et al., 2009), which can be fruitfully addressed in future studies. One reasonable extension of the present work would include an increase of the number of learning trials during the acquisition phase or a decrease in reward value, which may allow to monitor the development of inhibition across different response systems, including instrumental behavior. Overall, the significant contribution of the third experiment lies on a conceptual level as the results provided considerable evidence for the presence of inhibitory stimulus control in human incentive motivation and, in analogy, drug addiction. This emphasizes the necessity to investigate drug-conditioned inhibition in the lab to enhance our preclinical understanding of drug-related learning and to correlate it with proximal measures of addictive behavior. Finally, such an approach may be useful to enhance our knowledge of the learning processes involved in the formation of drug cues in the natural environment or in the prevention of cue reactivity from its expression.

In sum, the third study of this thesis is the first which investigated the development of reward conditioned inhibition across three different affective response systems (e.g., Lang et al., 1998; Mauss & Robinson, 2009). The results provided evidence for the retarded acquisition of excitatory conditioned subjective and physiological responses by a discriminative I^{Δ} previously predictive for the non-availability of reward. These data further support the notion that the association of stimuli with the non-availability of reward may give rise to conditioned inhibition in the human. This is relevant for our understanding of stimulus control of reward-directed responding in general and in particular with regard to clinical disorders like drug addiction, where the processing of reward and reward predictive stimuli has gone astray.

Finally, all conditioning studies of this thesis revealed pronounced dissociations between physiological measures of motivational valence and reports of subjective pleasure. Although the mediation of overt drug seeking or intake behavior by appetitive conditioning processes was not the topic of this thesis, especially the results of the two smoke-conditioning studies may be interesting in light of recent discussions of the functional role of subjective pleasure in the motivation for drug (Hogarth et al., 2010; Hogarth & Duka, 2006). According to incentive theories (Bindra, 1974; Stewart et al., 1984; Wise & Bozarth, 1987; see also Toates, 1994), drug-predictive stimuli are hypothesized to evoke an appetitive central state, mediating approach and motivating instrumental drug seeking behavior. Although these theories do not necessarily focus on subjective pleasure as they are rooted in animal research, most commonly drug cues are hypothesized to evoke subjective craving and pleasure in humans. In direct contrast, the participants of the first study of this thesis failed to report cue-evoked craving (Field & Duka, 2001; Hogarth et al., 2003a) or pleasure (Lazev et al., 1999) as found in previous smoke-conditioning studies. However, there was clear evidence for the acquisition of preparatory physiological responses. Thus, these results appear to be more in line with incentive sensitization theory (Berridge & Kringelbach, 2008; Berridge & Robinson, 2003; Robinson & Berridge, 1993), which proposed distinct dissociations between the motivational and hedonic effects of drug stimuli and their representation in conscious awareness. However, the lack of subjective report may have resulted from a decreased (cognitive) expectancy to smoke (Bailey et al., 2010; Field & Duka, 2001; McBride et al., 2006), as the rating data were assessed after conditioning. The second experiment of this thesis may tentatively support this conclusion, as the subjective data were collected during conditioning. Although the second study demonstrated intact stimulus control of craving, the CS+ for smoking evoked less pleasure, which was evident during the end of conditioning only (although the pleasure scores were still above the "neutral" midpoint of the scale). In direct contrast, both studies revealed evidence for the acquisition of appetitive conditioned responding to a previously neutral stimulus or a smoking cue. Although these results have to be interpreted cautiously, as they may comprise an interaction of stimulus type, learning and satiety, they are interesting for several reasons. First, one may consider the decrease in self-reported pleasure evoked by the CS+ during the second study as indication of a satiety induced attenuation of the incentive value of smoking (Bindra, 1974, 1978; Robinson & Berridge, 1993; Stewart et al., 1984; Toates, 1994). This would be in accordance

with the overall decrease in craving found in both studies. However, stimulus-control of craving apparently remained intact[10]. Moreover, previous studies manipulated deprivation experimentally (e.g., via nicotine patch or smoking abstinence), yet reported similar results (Bailey et al., 2010; Geier et al., 2000; McDonough & Warren, 2001; Mucha et al., 1999; Tiffany, Warthen, & Goedeker, 2009; Waters et al., 2004; but see also McClernon, Kozink, Lutz, & Rose, 2009; McClernon, Kozink, & Rose, 2008). Interestingly, a cue reactivity study conducted by Drobes and Tiffany (1997) revealed results comparable to those received for the conditioning of a smoking cue in the second study of this thesis. In this study, cue exposure increased craving and negative affect, although the facial EMG of the zygomatic and corrugator muscles revealed evidence to the contrary. Deprivation resulted in a general increase in craving only, yet failed to enhance the incentive value of the smoking cues (although skin conductance during cue exposure was partially increased). Thus, to account for the emergence of negative affect Drobes and Tiffany (1997) discussed their results in light of a previously proposed cognitive model of drug craving (Tiffany, 1990). This model conceptualizes craving and negative affect to emerge from non-automatic, cognitive processing whenever automatic drug use routines are blocked (which functions to foster or impede the execution of the action schemata when smoking is not available or explicitly avoided in an attempt to reach abstinence, respectively). Thus, during this study cue-evoked craving and negative affect may have emerged as cigarette smoking was not available (see also Bailey et al., 2010; Carter & Tiffany, 2001; Sayette et al., 2003).However, this interpretation can probably not account for the present results, as smoke reinforcement was available immediately. Thus, one may consider subjective pleasure as a particular sensitive index of the current incentive value of smoking. However, this raises the question why the other measures were apparently less affected. Alternatively, one may consider the role of satiety in the present protocol as marginal. Indeed, incentive sensitization theory (Berridge & Kringelbach, 2008; Berridge & Robinson, 2003; Robinson & Berridge, 1993) may provide a more parsimonious explanation for the emergence of unpleasant affect, as the theory suggests that "with the development of an addiction drugs become pathologically wanted ("craved") and this can occur even if drugs are liked less and less" (Robinson & Berridge, 2001, p. 110). Although Robinson and Berridge (1993) stated hedonic "liking" as not equitable to "wanting", hedonic

[10] Additional analyses of the rating data with each conditioning block divided into two sub-blocks revealed the same results.

and motivational systems are often closely interlinked. For instance, Winkielman et al. (2005) presented positive facial expressions subconsciously and found enhanced beverage wanting and consumption. Interestingly, both smoke conditioning studies of this thesis revealed evidence for the acquisition of an implicit positive affective response to neutral stimuli or smoking cues predictive for an opportunity to smoke. Although facial muscular activity is certainly not identical to overt behavioral approach, the increased orbicularis oris response may indicate the motor priming of consummatory intake behavior (Müller et al., 2003). Thus, the present results may argue for the partial independence of conscious pleasure and implicit hedonic responses and suggests the relationship between subjective and objective measures of motivation for drug as valuable for further research.

FUTURE DIRECTIONS

Several topics emerged during this thesis as fruitful targets for future studies. First, physiological measures have been proven as an useful tool for the investigation of the motivational basis of reward-conditioned responding. In particular, the application of facial EMG allowed to reveal evidence for the acquisition of appetitive and consummatory smoke conditioned responses, which crucially extends previous work (Drobes & Tiffany, 1997; Geier et al., 2000; Hogarth et al., 2003a; Hogarth & Duka, 2006; Lazev et al., 1999; Mucha et al., 1998). Moreover, as the EMG of the M. orbicularis oris qualified as sensitive index of consummatory response tendencies, a special emphasis should be given to the further development of this measure. Thus, it may be interesting to probe cue-evoked motor priming of consummatory responses in picture based free-viewing paradigms. Furthermore, it may be important to investigate the dependency of these responses on the proximity of smoke reward. This can be reached by manipulations of stimulus content (e.g., BEGIN vs. END stimuli), stimulus duration (e.g., long vs. short CS-US intervals) or probability of reinforcement (see below).

As the conditioning studies of this thesis revealed considerable evidence for an appetitive nature of excitatory conditioned smoking cues, further research may benefit from a stronger focus on individual differences in the acquisition or expression of cue-evoked responding. This is important for several reasons. First, prominent theories diverge in their emphasis of incentive motivational processes in the control of compulsive drug seeking and drug taking (Everitt & Wolf, 2002; Koob & Le Moal, 2005; Robinson & Berridge, 1993; Siegel et al., 2000; Stewart et al., 1984; Tiffany, 1990). According to Robinson and Berridge, neural systems critically involved in the attribution of incentive salience to drug-related cues become sensitized after repeated applications of addictive agents (Berridge & Kringelbach, 2008; Berridge & Robinson, 2003; Robinson & Berridge, 1993). Thus, the incentive motivational effects of drug stimuli are assumed to escalate during the progression of recreational drug use to compulsive behavior. In contrast, chronic self-administration may promote the formation of intractable stimulus-response habits (Everitt & Wolf, 2002; Robbins & Everitt, 1999) or automatized drug use action-schemata (Tiffany, 1990), thereby undermining voluntary control. Thus, in highly addicted individuals stimulus control of addictive behavior may be less dependent on incentive motivational effects. So far, only few studies compared

the reactivity of heavy vs. light smokers with physiological measures of motivational valence and revealed diametrically opposite results. For example, Cui et al. (2012) reported a greater attenuation of cue-modulated startle in heavy smokers. In contrast, Rehme et al. (2009) used the startle-paradigm and found stronger appetitive effects of smoking stimuli in light smokers (see also Coggins, Murrelle, Carchman, & Heidbreder, 2009; Hogarth, Mogg, Bradley, Duka, & Dickinson, 2003b; Vollstädt-Klein et al., 2011, for further studies on differences between light and heavy smokers). Accordingly, it may be fruitful to investigate the reactivity of smokers varying in the degree of dependence in cue reactivity paradigms or to probe their propensity to acquire smoke conditioned appetitive responses.

Moreover, there is considerable evidence from animal research that individuals may differ in the degree their behavior is under the motivational control of (Pavlovian) conditioned excitatory cues. In a series of studies Robinson et al. (as reviewed in Saunders & Robinson, 2013) showed that reward conditioned stimuli acquire motivational significance particular in a subgroup of animals (so called "sign-trackers"). Thus, in some rats a lever-CS for (food) reward evokes a "sign-tracking" response (i.e., conditioned approach and "fondling" of the lever, which frequently mirrors the consummatory responses directed to the reward). In contrast, in other animals the same CS evoke a "goal-tracking" response (i.e., after an initial glance at the CS the animals directly approach the location (food cup) were the reward is delivered). Moreover, only in sign-trackers the CS acts as efficient conditioned reinforcer (Robinson & Flagel, 2009), although it is equally "predictive" (Rescorla, 1988) for reward in both groups (see also Flagel et al., 2011; Tindell et al., 2005). Furthermore, in these animals drug cues are more attractive (Yager & Robinson, 2013) and (reinstatement of) cocaine self-administration is stronger dependent on cue presentation (Saunders & Robinson, 2010) or drug priming (Flagel et al., 2011). Finally, "sign-trackers" appear to be especially prone to develop cocaine-induced psychomotor sensitization after repeated treatment (Flagel, Watson, Akil, & Robinson, 2008). Thus, individual variations in the tendency to attribute incentive salience to reward predictive stimuli may form a disposition for the development of addictive behaviors in humans. Furthermore, treatment seeking high "cue-reactors" may benefit especially from cue exposure treatments (Mahler & de Wit, 2010; Saunders & Robinson). Accordingly, it is important to identify these hyper-responsive individuals, which can be reached by correlating the incentive-motivational effects of cues for drug and natural rewards. For instance, Mahler and de Wit (2010) found that those smokers who reported the

highest cue-evoked craving to smoke when deprived from smoking also reported the highest cue-evoked craving for food when deprived from eating (see also Styn, Bovbjerg, Lipsky, & Erblich, 2013). Thus, it may be promising to investigate whether (preselected) smokers with the highest affinity to cues for smoking (as measured by facial EMG or the affect-modulation of the startle-response) also show the highest appetitive response to cues for food. Moreover, it may be important to probe the motivational impact of smoking cues on instrumental drug seeking in high-reactive smokers. Thus, "cue-reactors" may show enhanced Pavlovian-instrumental transfer as smoking cues are highly motivating in those smokers. Moreover, as this subgroup may be characterized by a general tendency to approach reward predictive stimuli, one may hypothesize an increase of outcome-independent, emotional Pavlovian-instrumental transfer (Balleine & Killcross, 2006; Corbit & Janak, 2007; Dickinson, 1997; Nadler et al., 2011; and see also the discussion of Experiment 3). As there is evidence that drug seeking can be "goal-directed" in some smokers in the sense that it is controlled by a specific expectancy of the reinforcer as revealed by outcome-specific Pavlovian-instrumental transfer (Hogarth & Chase, 2011, 2012; Hogarth et al., 2007), "sign-trackers" may be characterized by an abolishment of goal-directed control. Finally, it may be important to discriminate both groups on the basis of conditioning paradigms more akin to those used in the animal literature. This may be helpful for eliminating confounds arising from the use of naturalistic picture stimuli and preselected samples (Mahler & de Wit, 2010). Interestingly, this phenotype may also be relevant for our understanding of terminal stimuli, as "sign-trackers" may not respond to the lack of a drug goal presumably encoded in terminal stimuli.

Regarding terminal stimuli and inhibitory conditioning processes in drug addiction, the consequent next step comprises the inclusion of neutral stimuli in the smoke-conditioning paradigm of the second experiment of this thesis to further substantiate putative inhibitory properties of END stimuli. Moreover, it may be fruitful to investigate the effects of instructed expectancies (Mechias et al., 2010; Phelps et al., 2001) to smoke on the reactivity evoked by BEGIN and END stimuli. This allows to test for the specificity of the effects of the expectancy manipulation by including emotional control material. Such an approach is generally important as the expectancy to smoke is considered as a significant determinant of cue reactivity (Bailey et al., 2010; Carter & Tiffany, 2001; Dols et al., 2002; McBride et al., 2006; Wertz & Sayette, 2001) and in particular interesting as END stimuli may specifically attenu-

ate the effect of the expectancy manipulation. Furthermore, previous research primarily focused on comparisons of smoking and neutral stimuli. Thus, it is unclear whether the expectancy to smoke specifically increases the responses to smoking stimuli or generally enhances the effects of arousing or appetitive stimuli. Interestingly, a recent study by Jones et al. (2012) with social drinkers found that the expectancy to receive alcohol also affected the responses to chocolate stimuli and vice versa. Thus, the expectancy to smoke may interact with a more general (appetitive) motivational state. In addition, putative inhibitory effects of terminal stimuli can be further probed by measuring their impact on drug intake behavior, especially under conditions of extinction (Davis & Smith, 1990; Davis & Smith, 2009; Hogarth et al., 2010; Müller et al., 2003; Rose, 2006; Schupp et al., 1999). Thus, in contrast to BEGIN stimuli, END stimuli are supposed to reduce the magnitude or duration of sham-puffing, which can be quantified with facial EMG of the M. orbicularis oris (Müller et al., 2003; Schupp et al., 1999). To control for voluntary counter-regulation, speeded reaction time tasks can be adapted to investigate the effects of both stimuli on the initiation of a (in-) compatible puffing response (Eisenbarth, Gerdes, & Alpers, 2011; Neumann, Hess, Schulz, & Alpers, 2005).

As the attentional effects of terminal and inhibitory conditioned stimuli were discussed several times during this thesis, further research should address this issue. In this regard, it may be promising to track the time course of attentional processing, as preliminary results suggest that END stimuli fail to engage early attentional allocation. This line of research is important, given a) that prominent theories make diametrically opposite predictions about (the function and) shifts in attention during conditioning (i.e., some theories propose an increase, e.g., Bindra, 1978; Mackintosh, 1975; Robinson & Berridge, 1993, others a decrease, e.g., Pearce & Hall, 1980, of attentional orienting towards a CS predictive of an incentive), b) the dissociable functions of early detection and sustained attention to drug stimuli in the mediation of drug seeking (i.e., early stimulus detection may be efficient for behavioral control under certain circumstances; see, for example, Hogarth et al., 2009), c) the assumptions underlying the usage of the "two-test strategy" in the examination of conditioned inhibition (i.e., to control for simple attentional explanations of apparent inhibitory effects; see, for example, Hearst, 1972; Papini & Bitterman, 1993; Rescorla, 1969; Williams et al., 1992) and d) the burgeoning interest into the attentional properties of inhibitory conditioned stimuli. For instance, a recent study by Miskovic and Keil (2013) reported that an

inhibitory conditioned (AB+/BX-) "safety signal" X failed to enhance sensory processing in comparison to an uninformative stimulus B, as indicated by steady-state visual evoked potentials (ssVEPs). Moreover, selective resource allocation to the shock-conditioned excitor A was apparently unaffected when presented in summation with the "safety signal" X or a novel stimulus C. Thus, the inhibitory trained stimulus failed to capture attention, although the participants acquired explicit knowledge of the experimental contingencies. Given that this paradigm was successfully used previously to demonstrate conditioned inhibition of fear-potentiated startle (Jovanovic et al., 2005), these results may suggest that inhibitory trained stimuli have functionally different effects on cortical sensory alertness and overt defensive behavior. Thus, from a functional perspective it may be beneficial for organisms to further pay attention to stimuli previously predictive of danger even in presence of stimuli indicating safety (see Miskovic & Keil, 2013). In contrast, a previous study conducted by Röskam and Koch (2006) found that in rodents feature-negative (A+/X->A-) shock-conditioning enhances prepulse inhibition to the feature X (i.e., the "safety signal"). As enhanced prepulse inhibition may indicate attentional modulation of sensorimotor gating (i.e., the protection of prepulse processing) these results suggest that the feature acquired the capacity to engage early attentional processing, which may be sufficient for behavioral modulation. Moreover, there is evidence that nicotine increases feature-negative conditioning (Macleod, Potter, Simoni, & Bucci, 2006), potentially by amplifying attentional orienting to the feature (MacLeod, Vucovich, & Bucci, 2010). Overall, these results emphasize the importance to discriminate between early and late stages of attentional processing and the need to address (functional) differences between several forms of inhibitory learning.

Finally, the present thesis emphasized the importance of temporal factors in the control of the motivation for drug use. Thus, the proximity and probability of drug reward are hypothesized to affect the nature of the conditioned response (see above: Core features of conditioning). This would be in accordance with previous research with appetitive and aversive reinforcers, which suggests that motivated behavior is functionally organized in sequences (Bindra, 1974; Bradley et al., 2001; Domjan, 2005; Fanselow, 1997; Konorski, 1967; Mobbs et al., 2007; Timberlake, 2001). From a modern ethological perspective conditioning is assumed to involve complete sets or constellations of behavior, which are functionally organized around biological goals (Bouton, 2007, p. 175). Behavior systems are hypothesized to be hierarchically divided into several subsystems and components engaged with

motivational processing and sensorimotor integration (e.g., Timberlake, 2001). Once a behavior system is engaged the goal aspects of the reinforcer determine the nature of the response dependent on the (physical) characteristics of the (conditioned) stimuli and the contextual information in the background (see also Mucha et al., 2008). A prominent example of a behavior system the reader may be familiar with is the one described by Fanselow et al. for antipredator defense (see, for example, Fanselow, 1994). This model incorporates three modes of defensive behavior, the "pre-encounter", "post-encounter" and "circa-strike" mode, which are dependent on predatory imminence. Thus, with an increase of the *proximity* or *probability* of threat, the behavioral repertoire of an animal shifts from pre-encounter defense to a state of heightened vigilance and freezing (post-encounter). This preparatory stage of defensive motivation may mirror what we refer to as anxiety in humans (see, for example, Bouton, Mineka, & Barlow, 2001)[11]. Finally, the circa-strike mode of defensive behavior is engaged when attack seems inevitable. This mode comprises overt fight-or-flight behavior and may be best described as a state of intense fear or panic. As the functional organization of defensive behavior in humans may mirror the one described in rodents in critical aspects, it is not surprising that elements of the model already found their way into human research. Based on work on physiological responses to affective picture stimuli, Lang et al. (e.g., Bradley et al., 2001) described a "defense cascade model" of human defensive motivation. This model assumes enhanced perceptual processing (general hypervigilance) as the dominant response during early stages of defense, which may be replaced by selective attention after threat detection. With increasing levels of activation, a cascade of (reflexive) responses unfolds in time accompanied by enhanced mobilization of resources and the priming of overt defensive behavior. Furthermore, threat imminence may shift the basis of neural processing from frontal areas to midbrain structures, including the periaqueductal gray, which has been implicated in the control of (active) avoidance and analgesic responses (e.g., Mobbs et al., 2007). Overall, this research suggests that a multiple measure approach may be valuable for the elucidation of the functional significance of human behav-

[11] Although this classification may be partially dependent on idiosyncratic preferences (see Bouton et al., 2001, p. 8; Davis, Walker, Miles, & Grillon, 2009, p. 106; Gerber et al., 2014, p. 247), there is considerable evidence for the existence of at least two different types of defensive motivation (anxiety vs. fear; e.g., Barlow, 2000; Blanchard, Yudko, Rodgers, & Blanchard, 1993; Davis et al., 2009; Fanselow, 1994; Grillon, 2008).

ior, as it allows to track divergent changes evoked by motivational stimuli in various response systems.

Moreover, from a clinical perspective elements of a behavior system approach have been incorporated into an elaborated associative model of the etiology of panic disorder (Bouton et al., 2001). Central to this model is the assumption that the experience of panic (i.e., a state of intense fear) supports the conditioning of anxiety (i.e., a preparatory state of apprehension) to stimuli preceding the attack. Furthermore, conditioned anxiety is assumed to potentiate (the next) panic attack, which may give rise to a vicious circle culminating into the development of a panic disorder. In particular, this model turned out to be useful as it met the criticism of previous conditioning theories by emphasizing a) the relevance of *interoceptive* conditioning processes (e.g., Dworkin, 1993), b) the dependency of the *form* of the conditioned response on the qualitative *nature* of the CS (e.g., Holland, 1977), c) the ability of conditioned stimuli to *modulate* or summate with the reactivity evoked by other stimuli and vice versa (Davis, 2006; Holland & Lamarre, 1984), d) the importance of *contextual* factors in the control of conditioned responding (e.g., Bouton, 2004) and e) the capability of conditioned stimuli to evoke (whole *sets* of) conditioned responses, which may be partially different from the ones evoked by the US (e.g., Hollis, 1997; Timberlake, 2001).

As this modern perspective on learning and defensive motivation significantly stimulated human research and theorizing, it may be fruitful to transfer core components of this approach to the study of appetitive and addictive behaviors. Considering the functional significance of motivated behavior and putative differences between natural and artificial reinforcers it may be premature to simply expect a parallel pattern of results to emerge. However, the consideration of the temporal position of a drug stimulus in the intake ritual may be a promising first step into the characterization of what might eventually be understood as an "addictive behavior system". As preparatory and consummatory behaviors may be differentially affected by incentive proximity, this type of research might provide an interface into the motivational organization of reward-directed responding (Akins, 2000; Bradley et al., 2001; Dickinson & Dearing, 1979; Fanselow, 1994, 1997; Konorski, 1967; Timberlake, 2001). Accordingly, future studies on smoking stimuli may benefit from manipulations of perceived reinforcer *proximity* (e.g., Löw, Lang, Smith, & Bradley, 2008), *probability* (e.g., Schmitz & Grillon, 2012), stimulus content (e.g., Conklin et al., 2008; Mucha et al., 1999; Yalachkov, Kaiser, Görres, Seehaus, & Naumer, 2013), duration (e.g., Lovibond & Colagiuri,

2013) and drug expectancy (e.g., Bailey et al., 2010; see also Mechias et al., 2010) as suggested above. Overall, this research may benefit from a multiple measure approach to the analysis of drug-related responding. In analogy to the animal literature (e.g., Akins, 2000; Timberlake, 2001) and the research described above, one may hypothesize preparatory motivational responses to emerge even in case of "distal" CSs of long duration or in environments associated with the reinforcer. For example, an environmental context associated with smoking may evoke heightened vigilance and general search behavior. After the detection of stimuli more proximal to smoking selective attention and approach may be the dominant responses, which might finally give rise to consummatory intake. In this regard it may be interesting whether the *form* of the CR depends on the *nature* of the CS. Although this type of research is in its infancy, there is considerable evidence stemming from animal research that the sensory characteristics of a CS affect the form of the conditioned response (e.g., Garcia & Koelling, 1966; Hollis, 1997; Timberlake & Grant, 1975). For example, in pigeons a localizable, illuminated key (CS) paired with food evokes a pecking response. In contrast, the presentation of a diffuse auditory CS results in an increase of general activity (e.g., Rescorla, 1988; see also Holland, 1977). Thus, in analogy to the sign-tracking literature, where a lever-CS supports approach and consummatory-like responses (e.g., Jenkins & Moore, 1973; Tomie, Grimes, & Pohorecky, 2008), it might be interesting to use small, localizable objects as CS, which may "afford" reach-to-grasp movements and object manipulation (e.g., Gibson, 1979; Tucker & Ellis, 1998). At least there is evidence from human data that the orientation of an object automatically activates compatible motor responses related to grasping (e.g., Symes, Ellis, & Tucker, 2007; Yalachkov, Kaiser, & Naumer, 2009). Moreover, regarding to the dependency of learning on temporal proximity recent human data support the notion that temporal contiguity might be less important for reward conditioned stimuli to acquire motivational significance (Lovibond & Colagiuri, 2013). In case of addictive drugs, there is evidence that environmental contexts (Conklin, 2006; Conklin et al., 2008) and stimuli related to the procurement of smoking (Mucha et al., 1999; Stippekohl et al., 2010) act as distal cues and evoke craving. In contrast, the acquisition or expression of consummatory responses may be more dependent on reinforcer proximity (Akins, 2000; Timberlake, 2001) and the second study of this thesis revealed preliminary evidence for this assumption.

Moreover, from a functional perspective stimuli from the terminal stage of smoking may be particularly suited to support learning based on the principles of homeostatic regulation (Mucha et al., 1999). Thus, END stimuli may be well prepared to evoke conditioned compensatory responses (Mucha et al., 1999; Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel, 1975, 1989), which may counteract the physiological disturbance produced by nicotine (e.g., nicotine induced arousal; see Clarke, 1987; Gilbert et al., 2000; Mucha et al., 1996; Niedermaier et al., 1993). Accordingly, it may be fruitful to probe the effects of END stimuli on nicotine, smoking (Rose, 2006; Rose, Behm, Westman, Bates, & Salley, 2003; Rose, Behm, Westman, & Johnson, 2000) or exercise (Daniel, Cropley, & Fife Schaw, 2006; Siegel, Krank, & Hinson, 1987; Taylor, Ussher, & Faulkner, 2007) induced arousal (e.g., as indicated by enhanced heart rate or skin conductance). Moreover, this approach may be valuable as it focuses on the ability of conditioned stimuli to affect or *modulate* the impact of the US, a theme probably more common to the drug literature. Furthermore, the responses evoked by drug stimuli may be modulated by extero- and interoceptive *contextual* factors (e.g., Bouton, 2000). The contextual modulation of cue reactivity is relevant for both basic and clinical research as cue exposure treatment may be enhanced by considering the context dependency of extinction (i.e., the renewal effect; see, for example, Conklin & Tiffany, 2002). Recent research already started to address this issue by investigating the effects of environmental contexts (e.g., Conklin, 2006) or satiation (e.g., Rose et al., 2003) on craving. In this regard it may be important that the smoking ritual itself comprises a plethora of multisensory stimuli (e.g., Bedi et al., 2011; Rose, Salley, Behm, Bates, & Westman, 2010; Rose et al., 2003; Yalachkov et al., 2013). Within the temporal context of the ritual, the interaction of these stimuli may be relevant for the control and probably termination of smoking. For example, there is considerable evidence that the sensorimotor components of smoking essentially contribute to its satisfying and satiating effects. Previous research showed that the intake of denicotinized smoke reduces craving and smoking behavior to a greater extent than a prior administration of intravenous nicotine (e.g., Rose et al., 2010; Rose et al., 2003). Thus, it may be reasonable to assume that conditioning processes contribute to the termination of smoking. In particular, taste stimuli may be a promising target for future research as the animal literature acknowledges a role of orosensory stimulation in the determination of meal size. Several studies demonstrated that the association with the later *interoceptive* effects of feeding may endow orosensory stimuli with condi-

tioned satiating effects, which may inhibit further consumption (e.g., Davis & Smith, 2009). The translation of this approach to the analysis of smoking behavior may give rise to the paradoxical situation that smoke conditioned stimuli may support both the *beginning* of intake and the *end* of consumption.

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