Normal and Pathological Visual Attentional Mechanisms in Psychiatric and Neurological Patients

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Summary

Visual attentional impairments, including both spatially lateralized and non-lateralized attentional functions, are commonly reported in psychiatric and neurological conditions. The first part of this dissertation presents two studies that were conceived as double-blind, randomized, sham-controlled trials to (i) assess the (to-be specified) sub-components of attentional deficits resulting from major depressive disorder (MDD) and, respectively, schizophrenia, and (ii) examined for (any) specific attentional benefits induced by a single session anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (dlPFC) in both patient groups compared to healthy controls. In MDD patients, parametric assessment of attentional functions yielded a significantly reduced rate of visual information uptake. Stimulating the prefrontal alertness system by means of tDCS ameliorated this deficit 24 hours after the stimulation. In terms of the neurophysiological basis, this effect on processing speed might be attributable to tDCS-induced N-methyl-D-aspartate receptor-dependent plasticity effects. On a larger-scale level, these after-effects may be indicative of tDCS-induced changes in the functional connectivity of fronto-parietal alertness networks, which enhance perceptual processing speed. Furthermore, they suggest that even a single session of tDCS over the dlPFC can give rise to lasting neuro-cognitive benefits resulting from an amelioration of cortical under-arousal beyond the time periods of unspecific tDCS-induced excitability increases. In schizophrenia patients, a reduced general attentional capacity in terms of both visual processing speed and short-term memory deficits were revealed to characterize attentional impairments. Concerning the efficacy of tDCS for improving cognition, results pointed to an interfering, rather than an ameliorating, effect of anodal prefrontal tDCS on practice-dependent improvements in processing speed. Thus, it cannot be ruled out that the stimulation parameters applied entail cognitive safety risks for schizophrenia patients. No tDCS-induced effects were found in healthy controls.

Study III reported in the second part of the dissertation was concerned with the behavioural consequences of selective attentional impairments in patients, with a focus on perceptual processing, specifically, on whether or not selective attention plays a role in visual grouping processes – a longstanding issue in basic attention research. This issue was addressed by examining whether the breakdown of selective attention in extinction patients (who suffer from a lateral bias of spatial attention) is associated with impairments in grouping operations. In more detail, using a visual search paradigm adopted from basic research, study III investigated how the patients would detect Kanizsa-type (grouped) target shapes in the presence of 'ungrouped' and partially grouped nontarget configurations (composed of the same elements). With single objects, patients did not perform significantly different from healthy controls. When confronted with a competitive search situation that presented multiple to-be-grouped items (of targets and nontargets), an extinction-specific spatial bias manifested in the patients characterized by preserved grouping in the right, attended hemifield and compromised grouping in the left, less attended, hemifield. This pattern points to a crucial contribution of selective attention to visual object integration processes.

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1 Introduction

Patients with psychiatric and neurological disorders commonly show deficits in visual attention. 'Visual attention' is defined as a set of cognitive processes controlling the selection of behaviourally relevant and inhibition of irrelevant information from cluttered visual environments. These attentional mechanisms are necessary as the capacity of our processing systems is limited – leading to a competition of visual objects for access to awareness (Broadbent, 1958; for review Desimone & Duncan, 1995; Kastner & Ungerleider, 2000; Schneider & Shiffrin, 1977).

Visual attentional processing has been conceptualised as being composed of different spatially lateralized and non-lateralized sub-components, or core functions, including spatial and non-spatial attentional selectivity processes, the speed of visual information uptake and the capacity of visual short-term memory (vSTM) (Bundesen, 1990, 1998). Conceivably, a breakdown in any of these sub-components may result in impaired attentional performance. However, the specific attentional sub-components underlying deficient cognition in various neurological and psychiatric disorders remain poorly understood. Further knowledge about affected sub-components is important for all endeavours aiming to develop reliable diagnostic methods and efficient treatment options for cognitive impairments. For example, based on (to-be-established) specific deficit profiles, those patients at risk of a greater degree of functional and behavioural impairment, and thus in need of specific treatment, can better be identified. Likewise, based on specific deficit profiles, a better distinction of various disorders in terms of neuro-cognitive deficits can be achieved.

Investigations targeting this issue can be informed by theories of normal attentional function (Peers et al., 2005). The 'Theory of Visual Attention' (TVA), originally proposed by Claus Bundesen (Bundesen, 1990), integrates the different attentional sub-components in a

unified quantitative model, thus providing a theoretical and computational framework for assessing behavioural attentional effects. Importantly, and in contrast to conventional neuropsychological tests, attentional assessment based on TVA is highly sensitive and can be used to quantify the different, specific attentional core functions in an independent manner.

Given this, TVA-based attentional assessment provides a suitable foundation, both theoretically and experimentally, for the aim of the first part of this cumulative dissertation: namely, to assess and modulate – by means of transcranial direct current stimulation (tDCS) – specific attentional impairments in patients suffering from MDD and schizophrenia, respectively.

The investigation of patients suffering from attentional disorders also provides a means to address general-psychological questions as to the role of attentional functions in normal information processing. That is, beyond clinical research, patients can be used as a model to examine normal attentional functioning by studying the consequences, and causes, of the failure of certain (core) functions in patients. One of the most prominent lines of research in this (neuropsychological) endeavour has focused on extinction patients, who suffer from unilateral deficits in selective attention after brain damage, which proved to be a useful approach for understanding normal attentional processes (e.g., Mattingley, Davis, & Driver, 1997; Conci, Böbel, Matthias, Keller, Müller, & Finke, 2009).

A long-standing question of basic attention research concerns the contribution of selective attention to visual processing mechanisms such as perceptual grouping. Grouping processes organize non-contiguous parts of the image into coherent entities by segmenting regions or by linking edge segments to form continuous object boundaries (e.g., Driver, Davis, Russell, Turatto, & Freeman, 2001; Koffka, 1935; Wertheimer, 1923). Both perceptual and attentional processes are relevant for perceiving a coherent, integrated world and, with regard to action control, these two constructs are assumed to be closely connected

(Gillebert & Humphreys, 2013). However, the relationship between selective attention and object integration by means of perceptual grouping is a topic of long-standing debate. Previous studies examining the contribution of attention in perceptual grouping have yielded inconsistent findings: some have proposed an involvement of selective attention (e.g., Treisman & Gelade, 1980), while others have argued that perceptual grouping occurs pre-attentively, in an automatic manner (Driver & Baylis, 1998; Gilchrist, Humphreys, & Riddoch, 1996; Scholl, 2001). On this background, the study presented in the second part of this dissertation was designed to explore the extent to which attention is required for object integration processes by means of perceptual grouping. More specifically, pursuing an approach that combined neuropsychological with general attention research, the study examined extinction patients with unilateral deficits in selective attention to assess whether perceptual grouping can occur without selective attention or whether it relies on the availability of attentional resources (Gillebert & Humphreys, 2013). – The following sections of the introduction will introduce the two parts of this dissertation in more detail.

1.1 Part one: Visual attentional dysfunctions in major depression and schizophrenia and their modulation by tDCS

In this section, the theoretical framework of the first part of this dissertation, based on Bundesen's Theory of Visual Attention (TVA), is outlined, with a focus on TVA's basic assumptions and neural interpretation. Sub-section 1.1.2 presents the background of studies I and II, outlining current research on visual attentional deficits in MDD and schizophrenia. Sub-section 1.1.3 presents the methodological approach taken by both studies, introducing the measurement of visual attention based on TVA and tDCS as potential means to modulate attentional (dys-)functions in patients and healthy humans. Finally, the aims and central research questions addressed by these studies are outlined.

1.1.1 Theoretical framework studies I and II: Theory of Visual Attention

1.1.1.1 TVA – its basic assumptions

The theoretical framework of attentional assessment in studies I and II is provided by Bundesen's Theory of Visual Attention (Bundesen, 1990, 1998; Bundesen, Habekost, & Kyllingsbaek, 2005) – a mathematical model conceiving visual attention as a multi-component process permitting the observer to select behaviourally relevant information (Vangkilde, Bundesen, & Coull, 2011). Conceptually, TVA is linked to the biased competition account (for review Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997). Accordingly, it assumes that the encoding of objects and their features for selection into a capacity-limited vSTM relies on a parallel-competitive race. In TVA, this process of encoding into vSTM is equivalent to making a perceptual categorization in terms of 'object x has feature i' or 'object x belongs to category i'. That is, when object x is selected, it is explicitly (in a reportable manner) recognized as possessing feature i or as being a member of category i. Thus, in contrast to other models of visual attention that consider stimulus selection and recognition as two processes operating successively (Broadbent, 1958; Deutsch

& Deutsch, 1963), TVA assumes a parallel, combined implementation of the two processes in the form of a competitive race.

As the vSTM storage capacity is limited to a few elements (Cowan, 2001; Luck & Vogel, 1997; Sperling, 1963), only those objects that win the race will be categorized, that is, encoded into vSTM. The competing objects' likelihoods (v) of winning the race are not equal; rather, for a specific object x, the likelihood depends on (i) the (bottom-up) sensory evidence (η) that object x is part of a certain category, (ii) the observer's attentional (i.e., perceptual decision) bias (β_i) and (iii) the attentional weight assigned to the object (w_x). The latter is determined by a pertinence value (π_j) reflecting the (top-down) importance of attending to objects of category j. This biased competition principle is expressed mathematically by TVA's weight and rate equations. The probability $v(x,i)$ that a categorization is encoded into vSTM is given by:

$$v(x,i) = \eta(x,i)\beta_i \frac{w_x}{\sum_{z \in S} w_z}$$

The first factor of the equation, $\eta(x,i)$, denotes the strength of the sensory evidence that element *x* belongs to category i. The second factor, β_i, denotes the perceptual decision bias associated with category *i* ($0 < \beta_i < 1$). The third factor reflects the relative attentional weight of object x, defined as the weight of object x, w_x, relative to the summed attentional weights of all other objects in the visual field *S*. The weight of object x, w_x, is calculated as:

$$w_x = \sum_{j \in R} \eta(x,j)\pi_j$$

Accordingly, the weight of object x is determined by the sensory evidence, $\eta(x,j)$, that object x belongs to category j of R, defining the set of all perceptual categories, and the pertinence value of category j, π_j, indicating the behavioural importance of attending to objects of category j. – A comprehensive mathematical description of TVA can be found

elsewhere (Bundesen, 1990, 1998; Duncan et al., 1999; Kyllingsbæk, 2006).

1.1.1.2 Neural Theory of Visual Attention

In general, visual attentional processing relies on the activity of a widely distributed network ranging from sensory areas in the posterior cortex to high-level regions in the parietal and frontal lobes as well as basal ganglia structures (for review Habekost & Starrfelt, 2009). This is in agreement with the neural TVA model (NTVA; Bundesen et al., 2005; Bundesen, Habekost, & Kyllingsbaek, 2011), providing a neural interpretation of TVA's rate and weight equations and asserting the significance of these brain structures for visual information processing. According to NTVA, the perceptual cycle progresses in the form of a two-wave process. During the first, pre-attentive wave of *unselective* processing, the objects' attentional weights are calibrated. During the second wave of *selective* processing, the most relevant objects, those with the highest attentional weight, are encoded into vSTM. More specifically, during the pre-attentive wave of unselective processing, sensory information is forwarded from the eye via the lateral geniculate nucleus (LGN) to visual areas in striatal and extrastriatal cortex where the sensory evidences η of the objects are computed. Multiplied by pertinence values π, arising from higher-order brain regions outside visual cortex, the resulting weighting signals are represented in a saliency map located in the broadly interconnected pulvinar nucleus of the thalamus. By dynamic remapping of receptive fields, cortical processing capacity is reallocated across the objects in the visual field in accordance with the computed weights w: the higher the attentional weight of an object, the more capacity (i.e., neurons) is allocated to it. Thus, attentional selection of an object during the second wave of processing directly arises from the amount of neurons, reflecting the attentional weight, allocated to that object (Bundesen et al., 2005). The resulting η values, multiplied by β values, determine the neuronal activation level (v) representing an object. As

soon as the vSTM map of locations, putatively located in the thalamic reticular nucleus (TRN), is set, objects in the visual field start to race for entry into vSTM. The fastest objects, that is, those with the highest ν values, will be encoded into vSTM. The latter is conceived as a feedback mechanism: neuronal activity representing the winners of the race is maintained by being incorporated into a feedback loop between sensory areas and the thalamus or frontal cortex (for review Habekost & Starrfelt, 2009).

In summary, TVA provides a mathematical formulation of normal visual attentional processing, integrating its different facets into a unitary framework. According to TVA, the perceptual cycle is completed in terms of an encoding race governed by the algebraic operations of the weight and rate equations. The NTVA provides an interpretation of these equations at the neuronal level, assuming that visual attentional processing is carried out by a distributed network ranging from sensory areas in the posterior cortex to higher-order regions in the parietal and frontal lobes as well as basal ganglia structures (for review Habekost & Starrfelt, 2009). The reliance on coordinated network activity makes visual attentional processing highly vulnerable to neural network abnormalities (Habekost & Rostrup, 2006), a characteristic feature of psychiatric conditions such as MDD and schizophrenia (e.g., Barch & Ceaser, 2012; Fornito, Yoon, Zalesky, Bullmore, & Carter, 2011; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Levin, Heller, Mohanty, Herrington, & Miller, 2007; Roiser et al., 2013).

1.1.2 Background to studies I and II: Visual attentional deficits in MDD and schizophrenia

Major depressive disorder and schizophrenia are serious mental disorders, arising from a complex interplay among predisposing genetic, environmental and personal vulnerabilities (Rutter, 2002; Tsuang, Stone, & Faraone, 2001). Cardinal symptoms of MDD include sustained depressed mood, loss of interest or pleasure, fatigue, feelings of guilt or

worthlessness, disturbed sleep or appetite. Schizophrenia is marked by hallucinations, delusions, disorganized speech or behaviour and negative symptoms (American Psychiatric Association, 2013). Next to these disorder-specific symptoms, patients often suffer from cognitive deficits, which partly remit, but sometimes persist even beyond depressive or psychotic episodes (Heaton et al., 2001; Schaefer, Giangrande, Weinberger, & Dickinson, 2013; Trivedi & Greer, 2014; Tyson, Laws, Flowers, Tyson, & Mortimer, 2006; Weiland-Fiedler et al., 2004).

Cognitive impairments in these patient groups include, but are not limited to, mnemonic, executive and space- and object-based attentional deficits, with the latter constituting core cognitive deficits (for review Elvevag & Goldberg, 2000; Nuechterlein et al., 2004; Rock, Roiser, Riedel, & Blackwell, 2014). Previous studies revealed below-average performance both in MDD and schizophrenia patients on various attention tasks such as simple reaction time (Egeland et al., 2003; Mialet, Pope, & Yurgelun-Todd, 1996), continuous performance (Egeland et al., 2003; Porter, Gallagher, Thompson, & Young, 2003), working memory span (Channon, Baker, & Robertson, 1993; Erickson et al., 2015; Johnson et al., 2013; Ravnkilde et al., 2002), and digit symbol coding tasks (Austin et al., 1992; Dickinson, Ramsey, & Gold, 2007; Knowles, David, & Reichenberg, 2010) as well as the Trail Making Test (Austin et al., 1992; Mahurin et al., 2006).

Despite being indicative of attentional deficits in MDD and schizophrenia, in these studies, the test performance cannot be straightforwardly related to more basic components of visual attention such as processing speed, vSTM or attentional selectivity. This is because these rather simple tasks – that, admittedly, can be applied in a time-economic fashion with minimal effort – lack good psychometric properties such as sensitivity or specificity. Instead, performance of these tasks is determined by multiple, hardly separable, cognitive functions. For example, in the Trail Making Test, different functional aspects, such as psychomotor

speed, visual search, executive and attentional components, all contribute to overall task performance (Salthouse, 2011). Likewise, in digit symbol coding tasks, efficient task performance requires both processing of visual information and fast motor actions. Therefore, a poor test result is a rather nonspecific finding that does not allow for fine-grained conclusions to be drawn about specific neuro-cognitive sub-mechanisms underlying the observed attentional deficits. A meaningful neuro-cognitive test, by contrast, would be expected to yield an unconfounded measure for a specific aspect (or aspects) of cognitive processing. Parameter-based attentional assessments based on Bundesen's TVA (Bundesen, 1990) constitute a method that meets these requirements – and that were therefore employed in the studies reported in the first part of the present dissertation.

1.1.3 Methodological approach studies I and II

1.1.3.1 Parametric evaluation of visual attentional deficits based on TVA

Combining the conceptual framework of Bundesen's TVA with simple psychophysical tasks – specifically, whole- and partial-report of briefly presented letters – allows the measurement of latent, mathematically independent parameters determining an individual's efficiency in visual attentional processing. In the typical whole-report task (illustrated in Figure 2A, p. 34), six letters are briefly flashed, either unmasked or terminated by post-display masking stimuli, on a computer screen and participants are instructed to verbally report as many letters as possible. For a detailed description of the whole-report task procedure, see studies I and II of this dissertation (pp. 32 et seq. and pp. 70 et seq.). By means of a (TVA model-based) fitting algorithm using the maximum likelihood principle (e.g., Ross, 2000), three mathematically independent capacity parameters of visual attention can be estimated from the behavioural data of the whole-report task, namely: (i) parameter *C*, the visual processing speed defined as the sum of the processing rates for all objects in the visual field ($C = \sum \nu$), (ii) parameter *K*, the storage capacity of vSTM in terms of the maximum number of objects that can be

maintained, in reportable form, at a given point of time, and (iii) parameter t_0, the minimum time, or threshold, for perceptual encoding (in milliseconds).

In the partial-report task (illustrated in Figure 2B, p. 34), participants are instructed to report pre-specified target letters that differ from distractors with respect to colour (target = red; distractor = blue). For a detailed description of the partial-report task procedure, see studies I and II of this dissertation (pp. 35 et seq. and pp. 73 et seq.). Based on the behavioural data generated in the partial-report task, two mathematically independent weighting parameters of visual attention can be estimated using TVA-based model fitting procedures, namely: (i) parameter α, the efficiency of top-down control, reflecting the allocation of attentional resources across targets and distractors (i.e., target-coloured and nontarget-coloured letters, respectively), and (ii) parameter w_λ, the spatial distribution of attentional weights across the left and right visual hemifields. A comprehensive account on the model fitting procedure is available elsewhere (Duncan et al., 1999; Kyllingsbæk, 2006).

Benefits of a parametric evaluation of visual attentional deficits based on TVA. In terms of practicality, the ease of implementing the TVA-based attentional assessment is a clear advantage of this approach. That is, estimates of distinct, core attentional parameters can be derived from performance in two psychophysical tasks within the same test routine with similar stimulus and response requirements. Furthermore, the simple instructions to perform the whole- and partial-report tasks as well as the non-speeded task responses (purely verbal reports) permit the assessment of patients with severe cognitive or motor impairments (Bublak et al., 2005; Duncan et al., 1999; Finke, Bublak, Dose, Müller, & Schneider, 2006). Methodologically, the good psychometric properties – in particular, high cognitive specificity of the estimated parameters – are a major strength of the TVA-based assessment (for review Habekost & Starrfelt, 2009). Mathematically independent fitting techniques yield precise quantifications of distinct, theoretically-grounded attentional parameters. In addition, based

on the neural model of the TVA (NTVA; Bundesen et al., 2005, 2011), an interpretation of the parameters at the neuronal level can be derived. This contrasts with most conventional neuro-cognitive tests, which are typically not grounded in a coherent theoretical framework and whose measures principally reflect task-specific and largely indistinguishable attentional demands – thus limiting their diagnostic potential with regard to revealing specific dysfunctions. Moreover, TVA-based measurement yields fairly consistent results both within and across test runs with low measurement error (Finke et al., 2005; Habekost, Petersen, & Vangkilde, 2014; Habekost & Rostrup, 2006). The method's sensitivity is another crucial advantage. Consequently, even minor cognitive deficits often missed by conventional methods can reliably be identified (Habekost & Rostrup, 2006), and even subtle performance changes arising from experimental manipulations, such as alertness modulations, can be picked up (Finke et al., 2010; Finke et al., 2012).

Taken together, these benefits render the TVA-based attentional assessment a valuable tool for studying attentional processing both in healthy persons and patients exhibiting attentional disturbances. A range of studies have already used this approach to investigate attentional processing in various clinical conditions, such as neglect (e.g., Duncan et al., 1999), dyslexia (e.g., Stenneken et al., 2011), neurodegenerative diseases (e.g., Redel et al., 2012) or neurodevelopmental disorders (e.g., Finke et al., 2011). However, despite the obvious benefits – in terms of theoretical grounding and cognitive specificity – of TVA-based attention assessment, prior to the present thesis work, there were no (published) studies that applied this approach in MDD and schizophrenia. Studies I and II of the present dissertation, for the first time, made use of this approach in these two major forms of psychiatric disorders, with the aim of (i) identifying attentional dysfunctions in these conditions in terms of a precise (TVA-based) parameter profile and (ii) examining for potential improvements in attentional processing by means of tDCS.

1.1.3.2 Transcranial direct current stimulation (tDCS)

Method and physiological mechanisms. During tDCS, a low-amplitude (0.5–2 mA) direct current, that is, a unidirectional flow of electric charge, is applied by saline-soaked sponge electrodes attached to the scalp to excite the underlying neural tissue (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). The principal physiological mechanism, generally inferred from studies of the primary motor cortex, is a shift in the neuronal resting membrane potentials (Bindman, Lippold, & Redfearn, 1964; Creutzfeldt, Fromm, & Kapp, 1962). Specifically, it was found that anodal (i.e., surface-positive) tDCS leads to a tonic depolarization of neurons, and hence increases neuronal spike activity. Cathodal (i.e., surface-negative) tDCS, by contrast, induces a hyperpolarization of neurons, and hence decreases neuronal spike activity. Consequently, this kind of bipolar stimulation modulates cortical excitability in an excitatory and inhibitory manner, respectively (Nitsche et al., 2003; Nitsche & Paulus, 2011). Stimulation effects are observable not only during, but also after, tDCS application as a function of stimulation duration and current intensity (for review Utz, Dimova, Oppenländer, & Kerkhoff, 2010). Even short stimulation durations of only 10 minutes were shown to induce enduring effects of about 1 hour in the human motor cortex (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). Such long-term effects of tDCS are ascribed to calcium-dependent plasticity changes driven by the glutamatergic system. Previous studies revealed that blockade of glutamatergic N-methyl-D-aspartate (NMDA) receptors, by the antagonist dextromethorphan, abolishes tDCS after-effects (Nitsche et al., 2003), whereas the NMDA receptor agonist D-cycloserine extends and calcium channel blockade abolishes the after-effects of anodal tDCS (Nitsche et al., 2003; Nitsche, Jaussi, et al., 2004; Nitsche, Liebetanz, et al., 2004).

Restoration of attentional dysfunctions in psychiatric conditions by tDCS. tDCS not only provokes regional effects underneath the electrodes, but also alters cortical network

connectivity between functionally associated areas (Polanía, Paulus, Antal, & Nitsche, 2011; Polanía, Paulus, & Nitsche, 2012). For example, in healthy humans, anodal tDCS of the left dlPFC was previously shown to induce a bilateral modulation of intrinsic fronto-parietal networks (Keeser, Meindl, et al., 2011; Keeser, Padberg, et al., 2011). Intrinsic activity in these networks plays an important role in a range of, particularly, alertness-dependent, cognitive processes (Clemens et al., 2011; for review Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Sturm & Willmes, 2001), and abnormal intrinsic fronto-parietal network activity is also discussed as underlying cause of attentional deficits in MDD and schizophrenia (Barch & Ceaser, 2012; Fornito et al., 2011; Kaiser et al., 2015; Levin et al., 2007; Roiser et al., 2013).

Owing to these neuro-modulatory properties, prefrontal tDCS is an interesting method to assess and modify the behavioural and physiological basis of cognitive processes both in healthy humans and patients suffering from psychiatric disorders (Shin, Foerster, & Nitsche, 2015). Specifically, modulating functional connectivity within compromised fronto-parietal networks via prefrontal tDCS might be a promising treatment option for restoring attentional dysfunctions in MDD and schizophrenia (for review Hoy & Fitzgerald, 2010; Mondino et al., 2014). Preliminary evidence suggests a beneficial effect of prefrontal tDCS on attentional tasks such as symbol-digit modalities tests or n-back tasks in MDD and schizophrenia (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014; Loo et al., 2012; Oliveira et al., 2013); still, the availability of data is scarce, not allowing definite conclusions. Moreover, these studies exclusively combined tDCS with conventional neuro-cognitive tasks possessing poor cognitive specificity and sensitivity. As such, these tasks are not appropriate to disentangle potential tDCS-induced effects on different cognitive sub-components like processing speed, short-term storage or top-down control processes, all controlled to some extent by prefrontal brain systems. Therefore, the basal cognitive ‘mediators’ of tDCS-induced benefits remain

unknown. On the one hand, the finding of prefrontal tDCS-induced changes in fronto-parietal alertness networks, implies that the beneficial cognitive effect should specifically result from a tDCS-induced increase of alertness levels (Keeser, Meindl, et al., 2011). On the other hand, considering that various cognitive functions rely on networks encompassing the dlPFC (Niendam et al., 2012), other modes of actions such as gains in short-term storage (e.g., for review Brunoni & Vanderhasselt, 2014) or attentional selectivity (e.g., Brosnan & Wiegand, 2017), are also possible as underlying the tDCS-induced cognitive benefits. Given this, combining tDCS with the cognitive highly specific, sensitive and theoretically-grounded TVA approach (Bundesen, 1990) may provide a good means to unravel even subtle effects of prefrontal tDCS on different neuro-cognitive parameters independently.

1.1.4 Aims and research questions studies I and II

The overall aim of the first two studies reported in this dissertation was to investigate and modulate the neuro-cognitive mechanisms underlying attentional deficits in MDD and schizophrenia. To this end, both studies were designed as double-blind, randomized, sham-controlled single-session tDCS studies that employed mathematical data modelling based on Bundesen's TVA in MDD and schizophrenia patients to address the following questions: *First*, what are the specific patterns of visual attention impairments in MDD and, respectively, schizophrenia arising from abnormal activation patterns within fronto-parietal networks? To establish this, TVA-based parametric attention assessment was used to isolate and quantify – potentially compromised – core attention functions in an unconfounded manner. The resulting attentional parameters were compared between each patient group and healthy controls. *Second*, does altering the neuronal activity patterns by anodal tDCS, applied to the left dlPFC (2mA), modulate specifically alertness-dependent attentional functions in MDD and schizophrenia or are other modes of action mediating possible benefits? *Third*, do patients and healthy participants respond differently to prefrontal tDCS? *Fourth*, how

enduring are potential tDCS-induced after-effects, that is, can they be observed 24 hours after stimulation, beyond time periods of unspecific excitability increases? To answer these questions, the two studies compared the effects induced by a single-session active tDCS to those induced by sham tDCS on the various TVA parameters both in patients and healthy controls across three time points: before, immediately after, and 24 hours after tDCS intervention.

1.2 Part two: On the contributions of selective attention to object integration processes

In the following section, the theoretical background of study III of this cumulative dissertation is presented by providing a brief overview of current research on the relationship between selective attention and object integration processes. Next, the rationale of the study as well as the methodological approach, based on visual search in parietal extinction, is described. Finally, the aim and central research questions addressed in this study are outlined.

1.2.1 Background to study III

The human visual system is equipped with mechanisms permitting the rapid, and apparently effortless, grouping of elements in complex visual scenes. These mechanisms organize unstructured or non-contiguous local elements into behaviourally meaningful representations, such as global forms or objects, by delineating regions with uniform properties or by linking (aligned) edges into object boundaries (e.g., Driver et al., 2001; Koffka, 1935; Wertheimer, 1923). This early process of perceptual organization is a pre-condition for the creation of a representation of the world with separable, integrated entities that can be efficiently acted upon. A central controversy in visual attention research concerns the involvement, or contribution, of selective attention to processes of perceptual grouping and object integration. Some studies suggest that only basic visual features are encoded automatically at pre-attentive processing stages, whereas attention is required to effectively bind parts into coherent wholes (e.g., Treisman & Gelade, 1980). In contrast, others propose that pre-attentive processes suffice to render and represent complete objects (Driver & Baylis, 1998; Gilchrist et al., 1996; Scholl, 2001).

Previous studies that have dealt with the role of selective attention in object integration principally fall into two main groups: (i) studies that employed visual search paradigms and (ii) studies that investigated patients with unilateral deficits in selective

attention.

The visual search task is a prominent paradigm in attention research (Duncan & Humphreys, 1989; Treisman & Gelade, 1980; for review Wolfe, 1994). The task requires observers to indicate, as rapidly and accurately as possible, whether a predefined target is present or absent in a display containing a variable number of nontarget, or distractor, stimuli. Visual search studies that examined whether object integration operates pre-attentively or requires selective attention often used an illusory 'Kanizsa figure', comprised of spatially discontinuous ('pacman'-type) components, as target stimulus (Kanizsa, 1976). The perception of an illusory Kanizsa figure as a single geometrical shape involves grouping operations, making this stimulus particularly suited for investigating object integration processes. In the relevant search studies, a Kanizsa target shape was presented among nontargets that were composed of the same 'pacman' inducer elements which were, however, rotated such as not to give rise to the percept of a coherent figure. By varying the number of nontargets and the target-nontarget similarity – by rotating the nontarget inducers to construct nontargets more (partially grouped) or less similar (ungrouped) to the target – the cognitive demands involved in target detection can be systematically manipulated. This renders the visual search paradigm useful for studying the role of attention (Fuller et al., 2006). The reaction time (RT) taken to decide whether a target is present or absent in the display can be plotted as a function of the search display size (i.e., the number of items in the display). The slope of the search function denotes the search rate, permitting inferences to be made about the time required to examine an individual item in the display. Based on this, it is possible to draw conclusions about search efficiency: A search function that rises only very slightly with increasing display size is taken to be indicative of efficient search processes operating spatially in parallel, or pre-attentively. In contrast, a linear increase of the search function is

indicative of the involvement of selective attentive processes in discerning target presence (e.g., Treisman & Souther, 1985; Treisman & Gelade, 1980).

The question whether selective attention is required to effectively bind parts into coherent wholes has not yet been resolved conclusively in the visual search literature. Whereas some studies reported evidence that Kanizsa figures are formed automatically by low-level, pre-attentive grouping mechanisms (Conci, Müller, & Elliott, 2007, 2009; Davis & Driver, 1994; Gurnsey, Humphrey, & Kapitan, 1992), others (Grabowecky & Treisman, 1989; Gurnsey, Poirier, & Gascon, 1996; Li, Cave, & Wolfe, 2008) found that searching for a Kanizsa figure among nontarget configurations led to RTs that increased with the number of display items – the implication being that selective attention is required for object integration.

Another line of research investigating the contribution of selective attention to processes of object integration is based on studying brain-damaged patients that exhibit a selective impairment of attentional mechanisms. For example, patients with right inferior parietal lobe lesions frequently demonstrate attentional deficits of hemispatial neglect and extinction (Karnath, Milner, & Vallar, 2002; Kerkhoff, 2001). That is, patients often fail to attend and respond to sensory stimuli located on the contralesional side of space, without necessarily suffering from any primary disorder of sensation or movement (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; for review Corbetta & Shulman, 2011; Heilman, Bowers, Valenstein, & Watson, 1987; Heilman, Watson, Valenstein, & Heilman, 1993). However, in extinction, hemi-inattention towards the contralesional, left hemifield occurs only when the visual system is burdened by the presence of multiple objects (Karnath, 1988; Riddoch & Humphreys, 1983). In particular, a contralesional item can be reported normally when presented in isolation, but the same stimulus is ‘extinguished’ or only poorly identified when accompanied by a competing ipsilesional stimulus (Bender, 1952).

Rather than resulting from a deficit in spatial orienting, it is suggested that a

competitive disadvantage for selection from the contralesional field, due to disrupted processes of selective attention, results in this striking phenomenon of extinction (Baylis & Driver, 1993; Humphreys, Romani, Olson, Riddoch, & Duncan, 1994; Ward & Goodrich, 1996). In line with this account of extinction in terms of a pathological, competitive bias against the contralesional hemifield (for review Desimone & Duncan, 1995; Kinsbourne, 1993), the lack of attention to stimuli on the left is not absolute, that is, it does not manifest as an all-or-none phenomenon. Rather, it reflects a relative difference, with substantially fewer attentional resources being allocated to the contralesional hemifield (see also Bays, Singh-Curry, Gorgoraptis, Driver, & Husain, 2010).

Despite this hemi-inattention, extinction patients are reported to have preserved access to integrated object information across the whole visual field (e.g., Driver, Baylis, & Rafal, 1992; Gilchrist et al., 1996; Ward, Goodrich, & Driver, 1994). Thus, for instance, studies revealed intact processing for object groupings and processes underlying figure-ground segmentation (e.g., Brooks, Wong, & Robertson, 2005; Conci, Böbel, et al., 2009; Driver et al., 1992; Gilchrist et al., 1996; Marshall & Halligan, 1994; Pavlovskaya, Sagi, Soroker, & Ring, 1997; Robertson, Eglin, & Knight, 2003; Ward et al., 1994). Stimulus segments that could be grouped across hemifields into a coherent object reduced extinction relative to an ungrouped stimulus – indicating that attentional deficits can be modulated by perceptual grouping. For example, a single-case study by Mattingley et al. (1997; see also Conci, Böbel, et al., 2009) reported preserved access to fragmentary bilateral stimulus segments only when these could be grouped across hemifields to form a Kanizsa square, but not when grouping was prevented. These results are indicative of early, pre-attentive integration of the elements into a (illusory) figure, which can be accessed despite extinction, that is, in the absence of selective visual attention (Ro & Rafal, 1996; Vuilleumier & Landis, 1998; Vuilleumier, Valenza, & Landis, 2001).

1.2.2 Rationale and methodological approach study III

As described in the preceding paragraph, previous studies addressing the role of selective attention in object integration either made use of visual search paradigms or investigated patients with unilateral deficits in selective attention. However, to our knowledge, no study has explicitly evaluated object integration processes in parietal extinction within a visual search context. That is, in the patient studies reviewed above, the typical stimulus displays consisted merely of a single grouped stimulus that had to be identified. Accordingly, from the patient studies, it is difficult to tell whether and how patients with extinction would benefit from grouping when being presented with multiple stimuli in the context of a visual search task. On the basis of the available work on extinction, it is not clear how visual search for an illusory figure would be affected by attentional impairments. On this background, the methodological approach adopted by study III of this dissertation was based on combining these two lines of investigation by examining object integration in visual search in patients with left-sided parietal extinction. Besides allowing a comparison between the two paradigms, employing a visual search task in patients does also provide a measure of performance in a more realistic scenario that affords higher ecological validity compared to a situation in which only a single item has to be identified.

1.2.3 Aims and research questions study III

Study III aimed to investigate the relationship between selective attention and object integration in a visual search task that presented to-be-grouped targets and nontargets to extinction patients with unilateral deficits of selective attention and healthy controls, respectively. Specifically, the effect of 'grouped' nontarget configurations that induced *partial* illusory shape groupings (in the left and the right visual field, respectively) was compared with the effect of symmetric but 'ungrouped' nontargets on the performance of visual search for Kanizsa target squares.

The following research questions were addressed: *First*, in patients with extinction, does partial shape information in nontargets reduce search efficiency in a manner similar to that seen in healthy participants (Conci, Gramann, Müller, & Elliott, 2006; Conci et al., 2007)? To address this question, we compared search performance for ungrouped nontargets with performance for partially grouped, that is, potentially interfering, nontargets. *Second*, how does the lateralization of attention in extinction affect search? That is, how do target-nontarget interference effects differ when partial shape information in nontargets is present in the less attended (left-grouped nontargets) versus the more attended hemifield (right-grouped nontargets)? To address this question, partial groupings in the left and, respectively, the right half of the nontarget items were systematically compared in terms of their relative costs on performance.

2 Original Studies

2.1 Study I: Single-session transcranial direct current stimulation induces enduring enhancement of visual processing speed in patients with major depression

In this paper, we report a double-blind, randomized, sham-controlled tDCS study that employed mathematical data modelling based on Bundesen's TVA in MDD patients to assess (i) the specific attentional functions affected in MDD patients compared to a healthy control group, (ii) the specific attentional benefits induced by a single session anodal tDCS over the left dlPFC, and (iii) the longevity of potential tDCS effects. MDD was found to be associated with a significantly reduced rate of visual information uptake. Furthermore, activating the prefrontal alertness system by means of tDCS ameliorated this deficit. These results imply that even a single session of anodal tDCS over the dlPFC has relatively enduring effects – even going beyond the stimulation intervention – on an attention function depending on intrinsic alertness, and more specifically on visual processing speed. By contrast, we did not find similar tDCS-induced effects in healthy control participants.

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2.1.1 Abstract

Attentional deficits are considered key cognitive symptoms in major depressive disorder (MDD) arising from abnormal activation patterns within dorsolateral prefrontal cortex (dlPFC) alertness networks. Altering these activity patterns with transcranial direct current stimulation (tDCS) might thus ameliorate alertness-dependent cognitive deficits in MDD patients. In a double-blind, randomized, sham-controlled study we investigated the effect of a single session of anodal tDCS (2 mA) applied to the left dlPFC on different parameters of visual attention based on Bundesen's Theory of Visual Attention (TVA; Bundesen, 1990) in a group of 20 patients with MDD and a control group of 20 healthy participants. The parametric attention assessment took place before, immediately after and 24 hours after tDCS intervention. It revealed a selective impairment in visual processing speed as a primary functional deficit in MDD at baseline assessment. Furthermore, a significant stimulation condition × time interaction showed that verum tDCS over the left dlPFC resulted in a processing speed enhancement 24 hours post stimulation in MDD patients. In healthy control participants, we did not find similar tDCS-induced effects. Our results suggest that even a single session of tDCS over the dlPFC can induce enduring neuro-cognitive benefits that indicate an amelioration of cortical under-arousal in MDD patients in a time frame beyond that of immediate excitability increases that are directly induced by the current.

2.1.2 Introduction

Attentional dysfunctions play a major role in patients with major depressive disorder (MDD) with respect to quality of life and clinical outcome (Paelecke-Habermann, Pohl, & Leplow, 2005; Watts & Sharrock, 1985). Furthermore, they are a major cognitive target in the dimensional approach to diagnosis and treatment according to the research domain criteria initiative of the National Institute of Mental Health (Insel et al., 2010). In this regard, transcranial direct current stimulation (tDCS) gained increasing interest as a non-invasive, safe treatment option with promising application not only for the clinical symptoms of MDD, but also for the restoration of cognitive functions (De Raedt, Vanderhasselt, & Baeken, 2015; Plewnia, Schroeder, & Wolkenstein, 2015).

TDCS modulates activity in specific brain regions by delivering weak direct current via two scalp electrodes with anodal and cathodal polarity. The immediate effect of anodal stimulation with standard parameters is a depolarization of the resting membrane potential of the stimulated neurons, and thus an increased neuronal excitability in underlying cortical regions (Bindman, Lippold, & Redfearn, 1964; Nitsche et al., 2008; Nitsche & Paulus, 2011; Utz, Dimova, Oppenländer, & Kerkhoff, 2010). However, even single tDCS sessions of only a few minutes can lead to more enduring effects lasting for several minutes to hours (Kuo & Nitsche, 2012; Nitsche & Paulus, 2000; Nitsche et al., 2003). As such so-called after-effects are, for example, reduced by the N-methyl-D-aspartate (NMDA)-receptor antagonist dextromethorphan, it is suggested that they are controlled by NMDA-dependent processes (Nitsche et al., 2003). Likewise, the partial NMDA agonist D-cycloserine was shown to prolong anodal tDCS-induced after-effects (Nitsche et al., 2004). TDCS also influences functional brain connectivity (Shin, Foerster, & Nitsche, 2015); particularly anodal stimulation over the left dorsolateral prefrontal cortex (dlPFC) was shown to stimulate resting state connectivity in bilateral fronto-parietal intrinsic brain networks in healthy adults

(Keeser, Meindl, et al., 2011). Importantly, the effects of anodal tDCS are assumed to be modulated by the initial degree of activation and connectivity in the stimulated network (Jacobson, Koslowsky, & Lavidor, 2012). These intrinsic networks encompassing fronto-parietal areas are strongly linked to the state of alertness (Clemens et al., 2011; Coull, Frackowiak, & Frith, 1998; Sturm et al., 1999), and therefore their potential modulation by means of tDCS might mainly affect alertness-dependent functions (Keeser, Meindl, et al., 2011) – and particularly so in MDD patients with postulated under-activated left dlPFC networks (Baxter et al., 1989; Coan & Allen, 2004; Fitzgerald, Laird, Maller, & Daskalakis, 2008; Grimm et al., 2008; Heller & Nitscke, 1997; Walter, Wolf, Spitzer, & Vasic, 2007). As alertness denotes the general level of reactivity and sensitivity to external stimuli (Posner & Petersen, 1990), it is particularly the speed by which stimuli are processed that is expected to be modulated by altering the state of alertness. In line with that, several studies, both in healthy controls and patients, reported that an increased state of alertness, e.g. by means of cueing or stimulant medication, led to faster visual processing (e.g., Finke et al., 2010; Finke et al., 2012; Matthias et al., 2010; Vangkilde, Bundesen, & Coull, 2011). The demonstration of modulations on the functional level would be important for estimating the potential clinical significance of those on the brain network level. However, single direct current stimulations will only result in small effects on cognition in healthy volunteers and patients (Berryhill, Peterson, Jones, & Stephens, 2014; Brunoni & Vanderhasselt, 2014), and therefore their assessment has to be based on sensitive tools. Furthermore, it might be possible that tDCS-induced alertness modulations result from multiple effects on diverse basic attentional mechanisms beyond processing speed, such as short-term storage or top-down control processes, all relying to some extent on prefrontal brain systems. Thus, measures that are applied to assess tDCS-induced benefits should be useful in disentangling these potential effects by indicating changes in each of these cognitive functions in a specific, distinct

manner. However, most previous studies on the effects of tDCS over the dlPFC in MDD patients assessed attention functions to monitor potential negative cognitive effects (Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013), and thus used time-economic screening tools that do not deliver such fine-grained information. For example, even though dlPFC stimulation was reported to improve performance of MDD patients in the go-no-go task (Boggio et al., 2007) and the symbol-digit modalities test (Loo et al., 2012), it is not clear what underlying more basal attentional mechanisms are mediating these benefits. In healthy adults, similarly, it was repeatedly reported that left dlPFC stimulation leads to better performance in the Sternberg task and n-back tasks, but as the cognitive specificity of these tasks is rather poor it is not possible to assess whether tDCS indeed increases alertness – and hence, accelerates the encoding of incoming information – or whether these benefits result from other modes of actions such as gains in short-term storage (Brunoni & Vanderhasselt, 2014; Fregni et al., 2005; Keeser, Padberg, et al., 2011; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Ohn et al., 2008; Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011). To summarize, it is challenging to characterise the precise neuro-cognitive modulations in attention functions that correspond to the tDCS-induced modulation on the brain network level. Furthermore, it is not clear whether (and how) MDD patients and normal participants respond differently to dlPFC tDCS.

In contrast to conventional neuropsychological tests, the parametric attentional assessment based on Bundesen's 'Theory of Visual Attention' (TVA; Bundesen, 1990, 1998; Bundesen, Habekost, & Kyllingsbaek, 2005) is highly sensitive and cognitively specific, and therefore enables explicit differentiations between specific attentional parameters defining the individual efficiency in visual attention processing: namely, perceptual processing speed (parameter *C*), visual short-term memory (vSTM) storage capacity (parameter *K*), and top-down control (parameter α). Employing two simple psychophysical tasks, whole- and partial-

report of briefly presented letters, TVA-based assessment allows extracting and exactly quantifying these different attentional parameters in a mathematically independent way, unconfounded by potential motor side effects, within the same tasks and with similar stimulus and response requirements (Bublak et al., 2005; Finke et al., 2010; Vangkilde et al., 2011). With these features, the TVA-based parametric assessment is optimally suited for the aim of this randomized, double-blind, sham-controlled study to assess whether – in agreement with previous reports of a close connection between alertness and the TVA parameter visual processing speed *C* (Finke et al., 2010; Finke et al., 2012; Matthias et al., 2010; Vangkilde et al., 2011) – a modulation of the fronto-parietal alertness network by means of single session of anodal tDCS is specifically associated with perceptual speed enhancements or alternatively accompanied, or even prompted, by other effects (i.e., changes in vSTM capacity and/or top-down control processes). Another aim of this study was to test the consolidation of potential after-effects beyond time periods where stimulation induces unspecific cortical excitability changes. For this purpose, the attentional parameters were assessed once 24 hours prior to tDCS, immediately afterwards and 24 hours post stimulation.

2.1.3 Methods

Participants

Twenty patients (11 male; age range: 22–48 years; mean age = 35.35; *SD* = 7.56) diagnosed with MDD (according to ICD-10: F32.1–3 and F33.1–3) were recruited from the Department of Psychiatry and Psychotherapy (LMU Munich). The patient screening, carried out by clinical psychiatrists, consisted of an assessment of psychopathological symptoms (Hamilton Depression Scale HAMD; Hamilton, 1960), disease severity (Clinical Global Impression Scale CGI; Guy, 1976), functioning (Global Assessment of Functioning Scale GAF; American Psychiatric Association, 2013) and a standardized test of hand preference

(Oldfield, 1971).

Participants with an IQ below 86 – as measured by means of the German Multiple-Choice Vocabulary Test (MWT-B; Lehrl, Triebig, & Fischer, 1995) – were excluded from participation, as well as those suffering from red-green colour blindness. Further exclusion criteria consisted of a history of seizures, pregnancy, metallic foreign body implants and enhanced/reduced scalp sensitivity. Additionally, patients with suicidal intent were excluded from participation. All patients were receiving stable antidepressant drug therapy during the study period. Medications were: Mirtazapine (n = 7, 7–45 mg/d), Venlafaxine (n = 8, 150–375 mg/d), Vortioxetin (n = 1, 5 mg/d), Bupropion (n = 1, 150 mg/d), Duloxetin (n = 1, 120 mg/d), Quetiapine (n = 3, 20–200 mg/d), Amitriptyline (n = 3, 25–150 mg/d), Opipramol (n = 1, 50 mg/d), Citalopram (n = 2, 20–40 mg/d), Escitalopram (n = 3, 10 mg/d), Sertraline (n = 1; 100 mg/d), Lithium (n = 1, 450 mg/d), Risperidon (n = 2, 0.5 mg/d), Aripiprazol (n = 4; 5–12.5 mg), Lorazepam (n = 6, 0.5–1.5 mg/d), Zopiclon (n = 2, 3.75–7.5 mg/d), Agomelatin (n = 2, 50 mg/d), and Pregabalin (n = 1, 150 mg/d).

The healthy control group consisted of 20 participants (10 male; age range: 22–48 years; mean age = 31.7; *SD* = 8.43) who were recruited from the same geographic area. None of the healthy control participants reported any (family) history of mental illness. All participants had normal or corrected-to-normal vision. The demographic details for each participant group, including information about IQ and handedness, as well as the clinical characteristics of the patients are summarized in Table 1. Participants provided written informed consent prior to the first experimental session and were compensated with 60€ for their participation. The study was approved by the LMU Munich Medical Faculty's ethical committee and conformed to the Declaration of Helsinki.

Table 1 Group Demographics and MDD Ratings.

	MDD Patients			Healthy Controls		
	Verum	**Sham**	***p***	**Verum**	**Sham**	***p***
Age	34.9 (9.37)	35.8 (5.75)	.80	30.8 (9.34)	32.6 (7.52)	.64
Gender (m/f)	6/4	5/5	.65	5/5	5/5	1.0
Handedness (r/l/a)	9/1/0	8/1/1	.59	9/1/0	9/1/0	1.0
Education (years)	11.2 (1.62)	11.6 (1.43)	.57	12.8 (.42)	12.9 (.32)	.56
MWT-B	105.3 (15.67)	103.4 (15.07)	.79	105.8 (14.48)	118.6 (20.81)	.13
Duration disorder (years)	5.7 (7.13)	4.49 (4.8)	.65	–	–	–
HAMD	18.5 (6.1)	19.8 (8.07)	.69	–	–	–
CGI	4.6 (.52)	4.5 (.53)	.67	–	–	–
GAF	54.3 (19.48)	53.1 (7.11)	.86	–	–	–

Note. Data are presented as means (standard deviations) or frequencies. MWT-B = German Multiple-Choice Vocabulary Test (Lehrl et al., 1995); HAMD = Hamilton Depression Scale (Hamilton, 1960); GAF = Global Assessment of Functioning Scale (American Psychiatric Association, 2013); CGI = Clinical Global Impression Scale (Guy, 1976); f: female; m: male; r: right; l: left; a: ambidextrous. P-values refer to a statistical comparison between the verum and sham condition.

Experimental procedure

Participants were randomly assigned to either the verum or sham tDCS condition by means of a computer-generated randomization list (https://www.random.org/lists/) for which the access during the study was restricted to two researchers (AH / WS). Neither the participants nor the experimenters were informed about the respective stimulation condition. Ten patients received verum left-anodal tDCS, the remaining 10 patients underwent sham tDCS. Similarly, 10 healthy control participants received verum tDCS and 10 healthy controls received sham tDCS. After being randomly assigned to the particular tDCS condition, participants underwent four experimental sessions each lasting between 60 and 90 minutes (see Figure 1). On session 1 (practice session), which could take place one to four days prior to the second test session, participants were familiarized with the TVA-based assessment and were trained on the respective tasks in order to avoid later practice effects. The following

three test sessions were conducted on consecutive days at about the same daytime each. On session 2 (baseline test), a baseline TVA-based whole- and partial-report assessment took place. On session 3 (post test), participants first obtained either verum 2 mA anodal or sham tDCS over the left dlPFC for 20 minutes and, directly afterwards, whole- and partial-report tasks were again applied. On session 4 (follow-up test), a follow-up assessment of the attentional parameters was conducted.

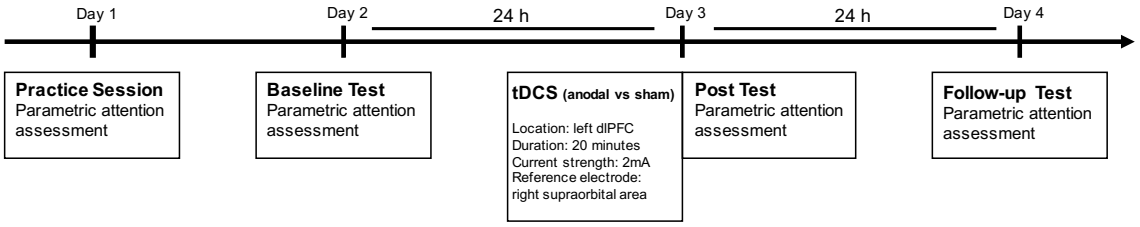

Figure 1 General experimental procedure.

TVA framework

TVA is a mathematical model, linked to the biased-competition account of visual attention (Desimone & Duncan, 1995). Accordingly, TVA assumes a parallel-competitive race of all objects and their features for selection into a capacity-limited vSTM store, representing what we consciously perceive and use for goal-directed actions. Access to vSTM depends on a speed criterion: only those objects processed fastest will enter the store and can become conscious (Bundesen, 1990). Object selection is thus determined by (1) its processing rate, and (2) the available size of the vSTM store, as a filled store no longer allows selection. Further, the probability of object selection into vSTM is defined by the attentional weight assigned to an object driven by both bottom-up factors such as stimulus saliency, as well as intentional, top-down determinants, such as task instructions. Consequently, only part of the objects will be represented within vSTM and will be accessible for further processing and goal-directed actions.

General method for whole- and partial-report

TVA-based testing was conducted in a dimly lit and sound-attenuated experimental laboratory room at the Psychiatric Clinic of the Ludwig-Maximilians-Universität München (LMU Munich). Within one test session, each participant completed the whole- and partial-report task, each lasting about 30 minutes. Task order was counterbalanced across participants. Stimuli were presented on a 27-inch PC monitor (1024 × 768 pixel resolution) with a refresh rate of 100 Hz. The distance between the monitor and the eyes of the participants was approximately 60 cm. In both tasks, each trial started with the presentation of a white central fixation point (diameter: 1 cm) for 1000 ms on a black background. Participants were instructed to keep fixation throughout the whole trial. After a delay of 250 ms, red and/or blue letters were briefly presented on a black background. The exposure durations were determined individually in a pretest to meet a criterion value. Stimuli consisted of target letters randomly chosen from a predefined set of the following letters: ABCDEFGHJKLMNOPRSTUVWXZ. On a given trial, a particular letter appeared only once. Stimuli were either masked, by a blue-red scattered square (≈1.5° visual angle) presented for 500 ms, or unmasked. In unmasked conditions, the effective exposure durations are prolonged by several hundred milliseconds due to visual persistence (Sperling, 1960). The participant had to report those letters she/he perceived with reasonable certainty, in arbitrary order and without speed stressing. The experimenter typed the responses on a keyboard and initiated the next trial by pressing the space bar.

After each block, participants received a visual performance feedback indicating the percentage of correctly reported letters out of all reported ones. Participants should aim for correctness between 70 and 90% by avoiding too conservative and too liberal responses. In total, the partial-report task consisted of 288 trials and the whole-report task of 140 trials, separated into blocks of 48 and 35 trials, respectively. Within each block, each display

condition was presented equally often in randomized order.

TVA-based whole-report. A representative whole-report trial is depicted in Figure 2A. On each trial, participants were briefly presented with six letters, either all red or blue, appearing on an imaginary circle with a radius of 6 cm (5.73° of visual angle) around the fixation point. The task of the participant was to identify and report as many letters as possible.

In order to individually adjust five exposure durations appropriate for the capabilities of a given participant, a pretest of four blocks of 12 trials each was performed prior to the main whole-report task in each test session. As in the main task, participants were instructed to report as many letters as possible. The exposure duration adjusting trials were organized in triples consisting of two 'easy' trials (i.e., one longer and one unmasked trial) and one adjusting trial in which initially, the six letters were flashed for 80 ms. If participants were able to report at least one letter correctly, exposure durations were decreased in steps of 10 ms until the lowest individual threshold, for which no letter could be reported anymore, was identified. Based on this threshold a corresponding set of four additional, longer exposure durations was chosen for the subsequent main whole-report task (e.g., 10, 20, 40, 90, and 200 ms). In these five conditions letters were masked. Additionally, in two unmasked conditions, letters were presented in the second shortest and the longest exposure duration condition. This resulted in seven 'effective' exposure duration conditions. In unmasked displays the effective exposure duration is prolonged due to the visual afterimage by a constant duration. This prolongation is defined by parameter μ (given in ms). This parameter is not relevant in the current study as it mainly serves the valid estimation of the parameters of interest. The patient group's average minimum exposure duration was 20.5 ms (SD = 7.59 ms) and did not differ significantly ($t(38) = .30$, $p = .77$) from that of the control group, which was on average 20 ms (SD = 0 ms). Within each block, the resulting seven different effective exposure

duration conditions were equally frequent.

Based on the performance in the whole-report task, the individual processing capacity aspects reflected by the TVA parameters perceptual processing speed *C* and vSTM capacity *K*, can be estimated by mathematical data modelling. The best-fitting TVA parameter values to the observed data of each participant were estimated by a maximum likelihood fitting algorithm described in detail by Kyllingsbæk (2006).

Performance (i.e., the number of letters reported correctly) was measured as a function of exposure duration. In TVA, stimulus processing is a dynamic process in which the probability for an object to be selected increases with increasing exposure duration. Presenting the stimuli with various exposure durations enabled us to examine the whole range of attentional performance aspects including both very early and late aspects of the participant's whole-report functions, thereby allowing a reliable model fit of the data (Finke et al., 2005). Within the TVA approach, an exponential growth function, relating the mean number of reported objects to the exposure duration, models the probability of stimulus identification. The growth parameter reveals the attentional processing speed (*C*), the rate at which stimuli are processed (measured in visual elements per second), and the asymptotic level of the function specifies the storage capacity (*K*), i.e., the maximum number of objects that can be registered in parallel and transferred into a vSTM store where information is kept online for a short period of time. The intercept of the curve with the x-axis describes the parameter perceptual threshold t_0, i.e., the individual *minimal* effective exposure duration in ms below which the number of correctly reported stimuli is zero (for illustration see Figure 3).

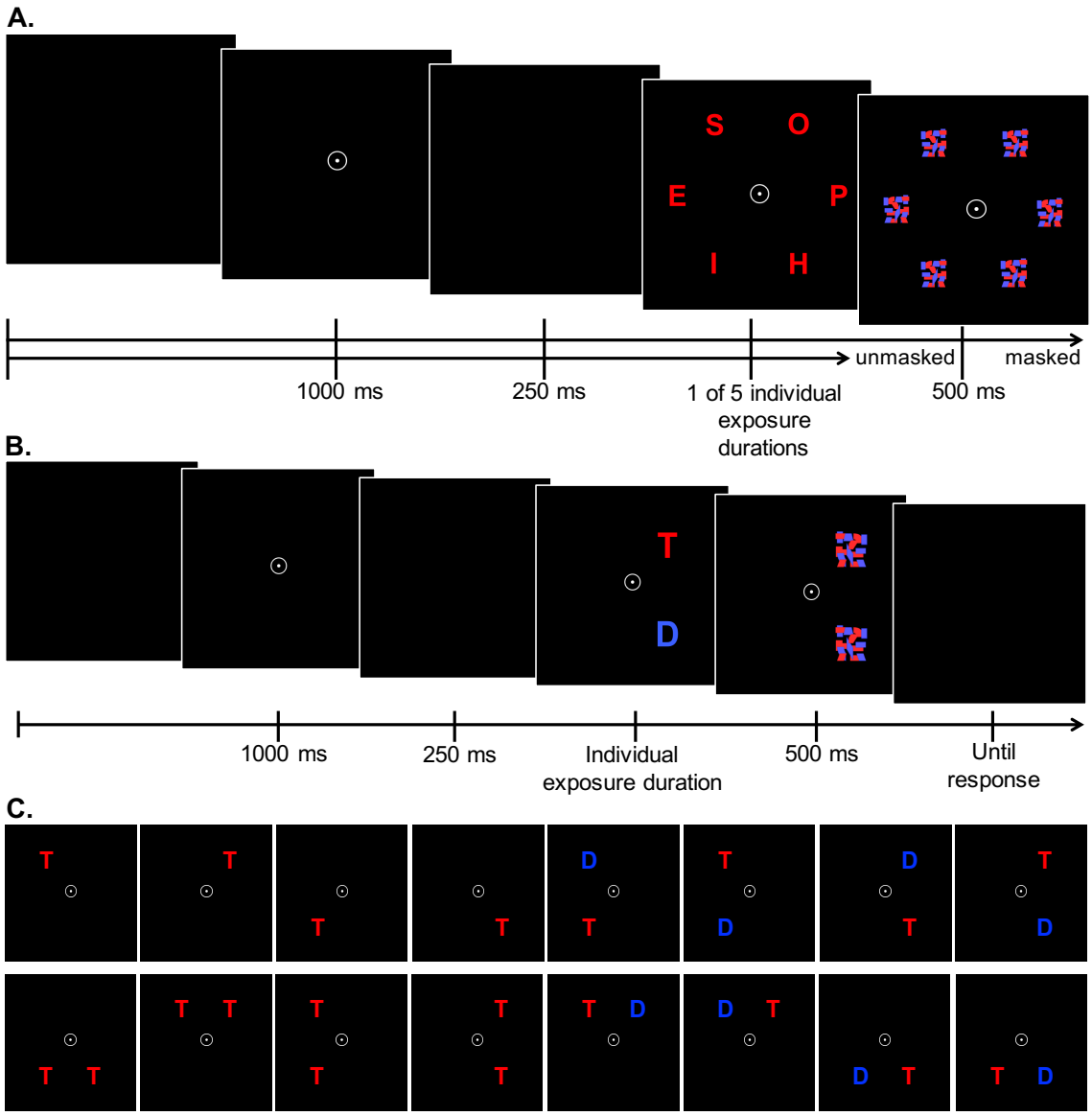

Figure 2 (A) Procedure used for the assessment of the TVA whole-report task. After the presentation of a central fixation point for 1000 ms and a brief delay of 250 ms, six letters are flashed in an imaginary circle either in red or blue font for one of five individually adjusted exposure durations (identified in a pretest). In these five exposure duration conditions, letters are masked for 500 ms. In two unmasked conditions, letters were presented in the second shortest and longest exposure duration condition. (B) Trial sequence and (C) display types of TVA partial-report task. After the presentation of a central fixation point for 1000 ms and a brief delay of 250 ms, one of the 16 possible display types appears for a predetermined individual exposure duration. Following that, presented stimuli (T = target = red letters; D = distractor = blue letters) are masked for 500 ms.

TVA-based partial-report. In the partial-report task participants were instructed to report predefined target letters, which differed from distractors with respect to colour (target = red; distractor = blue). In each trial, either a single target (letter) or a target plus distractor (letter) or two targets appeared at the corners of an imaginary square located 7.5 cm around the fixation point. All letters were masked for 500 ms. If two letters were presented on the display, they were either flashed in a row or in a column, but never diagonally.

In total, the partial-report task consisted of sixteen conditions, which were counterbalanced across all six blocks: target appearing alone (T; four possible alternatives: upper right/left or lower right/left corner), target appearing with distractor (T-D; eight possible alternatives), and two targets appearing together (T-T; four possible alternatives). For an exemplary partial-report trial sequence and all possible display types see Figure 2B and 2C.

As for the whole-report task, the exposure duration of the flashed letter(s) was individually determined for each participant prior to the main task. To that end, a pretest was performed: First, 24 trials with an initial exposure duration of 80 ms were presented. This was decreased by steps of 10 ms if participants were able to report two letters in the target-target condition. In contrast, if they could only name one of the two target letters, exposure duration was kept at 80 ms, and if none of the two targets could be reported, exposure duration was increased by steps of 10 ms until participants could name, on average, one letter per trial correctly. Subsequently, 24 trials were run and performance at the calculated exposure duration was checked for the different experimental conditions. If participants reported 70–90 % of the single targets (T) and at least 50 % of the dual targets (T-T) correctly, the exposure duration was kept for the main partial-report task. If not, exposure durations were increased or decreased manually by the experimenter and performance was rechecked in another round of 24 trials. The patient group's average exposure duration was

82.67 ms (*SD* = 27.14) and did not differ significantly ($t(38) = 0.85$, $p = .40$) from those of the control group that was on average 75.33 ms (*SD* = 27.69). Based on the performance in the partial-report task, the attentional selectivity parameter estimate (i.e., TVA parameter α) was derived from mathematical data modelling. From the probability of stimulus identification, attentional weights are derived for targets (w_T) and distractors (w_D). From these values one can draw inferences about the distribution of attentional resources across targets and distractors (Duncan et al., 1999), represented by the parameter top down control α. In formal terms this is expressed as the ratio of distractor (D) to target (T) weights: w_D / w_T. An α close to zero indicates high selectivity, i.e., targets receive more weight than distractors. Values of α close to 1 signify no selectivity.

Transcranial direct current stimulation

Transcranial direct current stimulation was delivered by a CE-certified direct current stimulator (neuroConn GmbH, Germany). Conductive rubber surface electrodes with a size of 35 cm^2 (5 × 7 cm) were covered with saline-soaked sponges and were placed on the scalp and the frontal head. For both verum and sham stimulation, the same electrode configuration was used with the anode placed above the left dorsolateral prefrontal cortex (dlPFC; F3 position according to the international EEG 10-20 system) and the reference electrode placed above the right supraorbital area. The F3-position has been linked to Brodmann areas 8, 9 or 46 on the medial frontal gyrus (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003; Homan, Herman, & Purdy, 1987) and this is representative for the left dlPFC. This electrode configuration is standardly used in physiological studies (e.g., Nitsche et al., 2008) and also in several behavioural studies this electrode montage was found to modulate cognitive parameters both in healthy participants and patients (e.g., Keeser, Meindl, et al., 2011; Palm et al., 2012). One stimulation session lasted 20 minutes during which constant current of 2

mA intensity was applied. To minimize the itching sensation at the onset of stimulation, current intensity was turned on in a ramp-like fashion until 2 mA was reached (15 seconds) and was ramped down correspondingly at the end of stimulation (15 seconds). In order to guarantee a successful blinding of participants, sham stimulation was performed in the same way as active stimulation, but the current was turned off after 45 seconds of tDCS so that participants could perceive the itching sensation at the beginning of the stimulation. Programming and encoding the stimulation routines in the stimulation device beforehand and by a person who was not the experimenter enabled a double-blind design in which both participants and experimenter were blind regarding the type of stimulation applied. Verum and sham stimulation was applied in different subgroups of participants. During the stimulation participants sat on a comfortable chair without being engaged in any task. As we were mainly interested in tDCS after-effects on attentional functions – both immediate and longer lasting ones of potential clinical relevance – tDCS was applied in an 'offline' protocol. Immediately after the tDCS intervention, patients completed the comfort rating scale, which is a self-rated questionnaire monitoring potential adverse effects resulting from the tDCS treatment (Palm et al., 2014).

Data analysis

For statistical analyses, IBM SPSS statistics version 22 was used. The level of significance was set to alpha = .05. Independent t-tests and χ^2-tests were used to compare groups with respect to demographic variables and clinical measures. In order to compare attentional parameters at baseline between the healthy control and the MDD patient group one-way analyses of variance (ANOVA) were conducted. In order to control for differences in education levels, these analyses were repeated using 'education' as covariate. Parameters at baseline in participants assigned to the verum vs. sham tDCS condition within these two

groups were compared by independent t-tests. To investigate the effect of tDCS on the attentional parameters at the three different time points, 2 × 3 mixed-factorial ANOVAs with the between-subjects factor stimulation condition (verum vs. sham tDCS) and the within-subjects factor time point (baseline, post and follow-up) were carried out separately for the healthy control and the MDD patient group. In order to assess the magnitude of the observed effects we measured Cohen's *d*, defined as the difference between two group means divided by the pooled standard deviation (Cohen, 1988). The integrity of blinding was assessed by means of χ^2-tests to compare participants' judgements of whether verum or sham tDCS had been applied between the verum and sham stimulation condition. Furthermore, independent t-tests were used to compare comfort ratings regarding the time during and after the stimulation between participants assigned to the verum and sham stimulation condition in the healthy control and the MDD patient group, respectively.

2.1.4 Results

Demographic and clinical characteristics

MDD patients did not differ significantly from the healthy controls with respect to age ($t(38) = 1.45$, $p = .16$), gender ($\chi^2(1) = 0.10$, $p = .75$), IQ ($t(38) = -1.47$, $p = .15$) and handedness ($\chi^2(2) = 1.03$, $p = .60$). However, there was a subtle, but significant difference between the healthy control ($M = 12.8$ years) and MDD patient group ($M = 11.4$ years) with respect to education level ($t(38) = -4.2$, $p < .05$). In both groups, participants receiving verum and sham stimulation did not differ significantly from each other with respect to any of the demographic and clinical characteristics (all ps $\geq .13$; see Table 1).

Baseline task performance – healthy control versus MDD patient group

Whole-report results

Figure 3 depicts the whole-report performance in terms of the mean numbers of correctly

reported letters as a function of the (effective) exposure duration in one representative MDD patient and healthy control participant. The curves represent the best fits from TVA to the observed data points derived by the maximum likelihood method (e.g., Kyllingsbæk, 2006). The TVA fitting procedure yielded fairly close fits to the observed scores. The predicted values accounted for r^2 = 93% of the variance of the observed mean scores. For each single participant, TVA model fitting yielded individual estimates for perceptual processing speed *C,* vSTM storage capacity *K* and the minimal effective exposure duration t_0.

Minimal effective exposure duration t_0. As depicted in Figure 3, below a certain minimal effective exposure duration t_0, participants were not able to report any letter correctly. Estimates of minimal effective exposure duration t_0 were basically comparable between MDD patients (*M* = 11.42 ms, *SD* = 11.55 ms) and healthy controls (*M* = 7.52ms, *SD* = 7.43 ms), as indicated by a non-significant main effect of group ($F(1, 38) = 1.84$, $p = .18$; see Table 2). The statistical results were confirmed when including 'education' as covariate ($F(2, 37) = .14$, $p = .71$). There was no significant correlation between the TVA parameter t_0 and 'education' neither in the healthy control ($r(18) = -.29$, $p = .22$) nor in the MDD patient group ($r(18) = -.22$, $p = .35$).

Perceptual processing speed *C*. Analysis revealed a significant main effect of group *(*$F(1, 38) = 11.82$, $p = .01$) indicating that processing speed was lower in MDD patients (*M* = 27.17 elements/second, *SD* = 10.16) than in healthy controls (*M* = 43.86 elements/second, *SD* = 19.18; see Table 2). Accordingly, in Figure 3, the MDD patient's whole-report function is characterized by a shallower slope in comparison to the control participant, indicating that the rate of information uptake at a given time unit is significantly reduced. The computation of Cohen's *d* yielded a large effect size (*d* = 1.1) and a nonoverlap of 58.9% in the two distributions of *C* scores. The statistical results were confirmed when including 'education' as covariate ($F(2, 37) = 6.28$, $p = .02$). There was no significant correlation between the TVA

parameter *C* and 'education' neither in the healthy control *(r*(18) = .23, *p* = .34) nor in the MDD patient group (*r(18)* = .09, *p* = .69).

Visual short-term memory capacity *K*. The main effect of group was not significant (*F*(1, 38) = 2.43, *p* = .13) indicating that vSTM was basically comparable between groups (see Table 2). Figure 3 accordingly illustrates that when exposure durations were increased, performance of the representative MDD patient and the representative healthy control participant reached an asymptotic value at approximately the same level. This value (*K*) is typically interpreted as the maximum storage capacity of vSTM (Sperling, 1967). In the present study, the mean number of items that can be represented was 3.67 (*SD* = .94) for the healthy control participants and 3.23 (*SD* = .85) for the patients. The statistical results were confirmed when including 'education' as covariate (*F*(2, 37) = .12, *p* = .74). There was no significant correlation between the TVA parameter *K* and 'education', neither in the healthy control (*r*(18) = .32, *p* = .18) nor in the MDD patient group (*r*(18) = .34, *p* = .15).

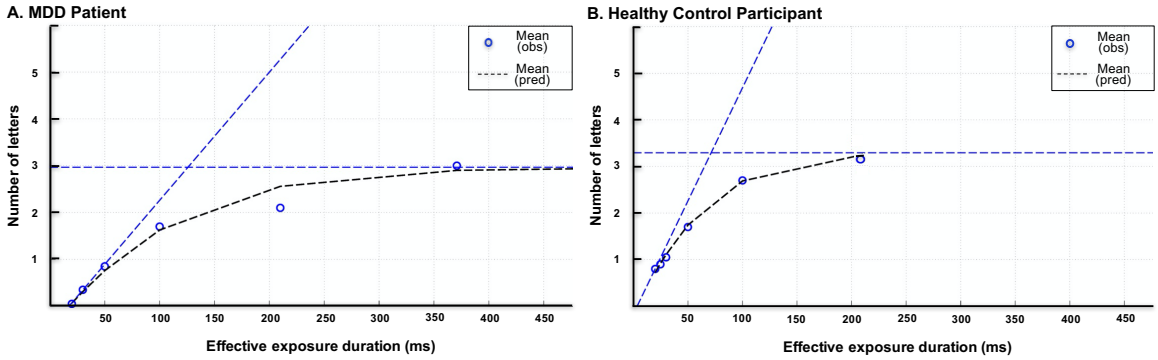

Figure 3 Whole-report performance (= number of correctly reported letters) of a representative MDD patient (A) and a healthy control participant (B) as a function of exposure duration. Circles show observed values (= obs), dashed lines represent the best fits of the observed scores by the applied model (pred = predicted). Maximum vSTM capacity *K* is indicated by the horizontal dashed line. The dashed slope line reflects processing speed *C*.

Table 2 TVA Whole- and Partial-Report Parameters at Baseline for the MDD Patient and Healthy Control Group

	MDD Patients		Healthy Controls		Statistical comparison
	Mean	***SD***	***Mean***	***SD***	***p***
C	27.17	10.16	43.86	19.18	.01
K	3.23	.85	3.67	.94	.13
t_0	11.42	11.55	7.25	7.43	.18
α	.46	.26	.36	.22	.21

Note. *C*: visual perceptual processing speed (elements/sec); *K*: visual working memory storage capacity (number of elements); t_0: minimal effective exposure duration; α: efficiency of top-down control.

Partial-report results

Based on the partial-report performance, the attentional selectivity parameter estimate, i.e., top-down control α, was derived from mathematical data modelling. The predicted data of the partial-report task fitted the observed data closely for each of the three conditions (single-target T, dual-target T-T, target-distractor T-D) as indicated by a mean Pearson product-moment correlation *r* of .95. The predicted values accounted for $r^2 = 90\%$ of the variance of the observed mean scores. Figure 4 depicts the mean partial-report accuracy of the MDD patient and the healthy control group, for the single target (none), the target plus distractor (D) and the target plus target (T) conditions across the left and right hemifield. A one-way ANOVA was performed to assess whether the two groups differ in top-down control.

Top-down control *α*. Analysis revealed statistically comparable estimates of top-down control in both MDD patients ($M = .46$, $SD = .26$) and healthy controls ($M = .36$, $SD = .22$) ($F(2, 37) = 1.77$, $p = .21$; see Table 2). The statistical results were confirmed when including 'education' as covariate ($F(2, 37) = 3.46$, $p = .19$). There was no significant correlation between the TVA parameter α and 'education' in the MDD patient group ($r(18) = .23$, $p = .34$). In the healthy control group there was a moderate positive correlation between

the TVA parameter α and 'education' ($r(18) = .50$; $p = .03$). From Figure 4 it can be inferred that, for both the patients and the healthy control participants, performance was highest in the single target condition ("none"). Adding a distractor (D) only slightly impaired performance, whereas adding a second target (T) noticeably reduced accuracy. Overall, the pattern of performance illustrates comparable top-down control in both MDD patients and healthy controls.

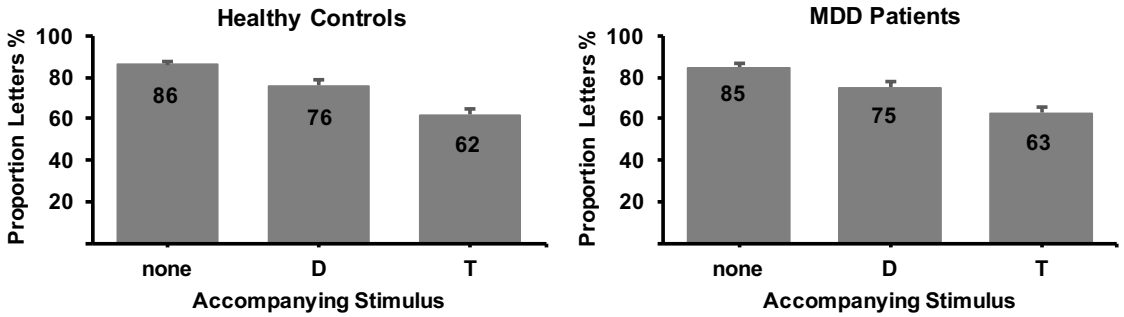

Figure 4 Mean partial-report accuracy (= percentage of correctly reported target letters) of healthy controls and MDD patients in the single target (none), the target plus distractor (D) and the target plus target (T) conditions across the left and right hemifield. Error bars reflect standard errors of the mean.

Immediate and enduring stimulation effects on attentional parameters

Healthy controls

At baseline, participants in the verum and sham group did not differ significantly with respect to any of the assessed TVA parameters (all ts ≤ 1.42, all ps $\geq .08$). Means and standard deviations are depicted in Table 3.

Whole-report performance. In order to assess immediate and enduring effects of tDCS on visual processing speed C and vSTM capacity K, separate 2 × 3 mixed-design ANOVAs with time point (baseline, post and follow-up test) as within-subjects factor and stimulation condition (verum vs. sham tDCS) as between-subjects factor were carried out. There was a significant main effect of time point on processing speed ($F(2, 36) = 4.05$, $p =$

.03, η_p^2 =.18) suggesting an increasing processing speed from baseline to post and then to follow-up test. The main effect of stimulation condition was not significant (p = .23). Most critically, the interaction between time point and stimulation condition was not significant ($F(2, 36)$ = .23, p = .80, η_p^2 = .01; see Figure 5), indicating that the difference between processing at different time points was not modulated by tDCS. Rather this finding suggests unspecific practice effects due to repeated testing with whole- and partial-report paradigms. For the parameters vSTM storage capacity K and minimal effective exposure duration t_0, no significant main or interaction effects were found (all ps ≥.12). See Table 3 for respective means and standard deviations.

Partial-report performance. For the parameter top-down control α, analysis yielded no significant main or interaction effect (all ps > .26). See Table 3 for respective means and standard deviations.

Table 3 TVA Whole- and Partial-Report Parameters in the Healthy Control Group for the Three Time Points (Baseline, Post, Follow-up)

		Baseline		Post		Follow-up	
	tDCS condition	***M***	***SD***	***M***	***SD***	***M***	***SD***
C	Verum	38.59	16.76	41.53	17.11	46.18	19.92
	Sham	49.13	20.84	54.69	22.49	56.09	28.29
K	Verum	3.47	.82	3.33	.84	3.48	.78
	Sham	3.88	1.04	3.86	.93	4.01	1.02
t_0	Verum	9.54	7.96	7.49	8.08	6.82	6.38
	Sham	4.96	6.43	6.80	4.11	3.77	4.82
α	Verum	.27	.20	.22	.26	.33	.16
	Sham	.45	.21	.42	.20	.39	.11

Note. C: visual perceptual processing speed (elements/sec); K: visual working memory storage capacity (number of elements); t_0: minimal effective exposure duration; α: efficiency of top-down control.

MDD patients

Analysis of variance yielded no significant baseline differences between MDD patients in the verum and sham tDCS group in any of the TVA parameters (all ts ≤ .74, all ps ≥ .47). See Table 4 for respective means and standard deviations.

Whole-report performance. The same mixed-factorial ANOVA as conducted for the healthy control group revealed a significant main effect of time point ($F(2, 36) = 4.21$, $p = .02$, $\eta_p^2 = .19$) and a significant interaction between tDCS condition and time point on processing speed ($F(2, 36) = 3.63$, $p = .04$, $\eta_p^2 = .17$) in the MDD patient group. Separate ANOVAs were computed for the two tDCS conditions to analyse the interaction. There was no main effect of time point in the sham group ($F(2, 18) = .23$, $p = .80$). In the verum group, the effect of time point was significant ($F(2, 18) = 8.51$, $p = .01$). Post-hoc testing with Bonferroni correction for multiple comparisons revealed that processing speed C did not differ significantly between baseline test ($M = 25.75$, $SD = 7.59$) and post test ($M = 26.22$, $SD = 9.02$; $p > .05$, 95% CI [−8.26; 7.32]), but at follow-up test ($M = 34.77$, $SD = 9.46$) it was significantly increased both compared to baseline ($p = .02$, 95% CI [1.51; 16.54]) and post test ($p = .01$, 95% CI [2.26; 14.84]; see Figure 5). An alternative analysis comparing the mean baseline-normalized performance both at the post test and the follow-up test between the two stimulation conditions (verum vs. sham) in MDD patients yielded a similar result: the analysis of covariance (ANCOVA) on the post test processing speed performance covarying the pretest performance revealed a non-significant main effect of stimulation condition ($F(1, 17) = .52$, $p = .48$; pairwise comparison 95% CI [−10.91; 5.34]; mean difference (verum vs. sham) = −2.79). The ANCOVA on the follow-up processing speed performance covarying the pretest performance revealed a borderline significant result ($F(1, 17) = 4.44$, $p = .05$; pairwise comparison 95% CI [−.010; 14.30] mean difference (verum vs sham) = 7.14), indicating that patients of the verum condition exhibited a greater mean increase in

processing speed than those of the sham condition. On average patients receiving verum stimulation could process about 9 elements/sec more (40%) at the follow-up compared to the baseline test and about 8 elements/sec (37%) more compared to the post test. These effects were large, as indicated by a value of Cohen's *d* of 1.1 (baseline vs. follow-up) and .9 (post vs. follow-up).

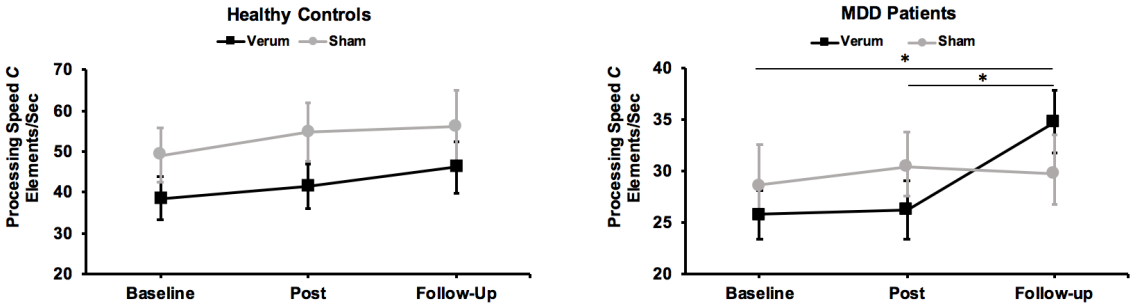

Figure 5 Effects of tDCS on mean perceptual processing speed *C* (measured in elements/sec) in healthy controls and MDD patients. Processing speed was assessed at baseline, directly after tDCS (post) and 24 hours after tDCS (follow-up).
Error bars represent standard errors of the means, * $p < .05$.

For the parameters vSTM storage capacity *K* and minimal effective exposure duration t_0, analyses yielded statistically non-significant effects (all *p*s ≥ .98). See Table 4 for means and standard deviations.

Partial-report performance. Analysis revealed a significant main effect of time point ($F(2, 36) = 3.24$, $p = .05$) for the parameter top-down control indicating that the efficiency of selection increased in both groups from baseline to post and from baseline to follow-up test. The time point × tDCS condition interaction was not significant ($F(2, 36) = .27$, $p = .76$), indicating that the stimulation did not modulate the increase in top-down control. See Table 4 for respective means and standard deviations.

Table 4 TVA Whole- and Partial-Report Parameters in the MDD Patient Group for the Three Time Points (Baseline, Post, Follow-up)

		Baseline		Post		Follow-up	
	tDCS condition	***M***	***SD***	***M***	***SD***	***M***	***SD***
C	Verum	25.75	7.59	26.22	9.02	34.77	9.46
	Sham	28.59	12.48	30.43	10.46	29.77	11.75
K	Verum	3.22	.84	3.39	.74	3.40	.70
	Sham	3.24	.90	3.29	.80	3.33	.71
t_0	Verum	13.35	14.10	7.44	5.78	11.86	6.79
	Sham	9.48	6.47	10.12	6.47	7.11	8.50
α	Verum	.46	.23	.40	.18	.32	.24
	Sham	.46	.30	.32	.19	.31	.13

Note. *C*: visual perceptual processing speed (elements/sec); *K*: visual working memory storage capacity (number of elements); t_0: minimal effective exposure duration; α: efficiency of top-down control.

Integrity of blinding and comfort rating

Of the MDD patients, 80% in the verum and 60% in the sham condition rated that they received verum stimulation. The distribution of sham and verum ratings did not differ significantly between conditions ($\chi^2(1) = .95$, $p = .33$). Of the healthy control participants, 70% in the verum and 30% in the sham condition rated that they received verum stimulation. The distribution of sham and verum ratings did not differ significantly between conditions ($\chi^2(1) = 3.20$, $p = .07$). Comfort ratings regarding the time during and after the stimulation did not differ significantly between participants in the verum and sham condition within the MDD patient group and healthy control group, respectively (all ts ≤ 2.01, all ps $\geq .06$).

2.1.5 Discussion

In the present study, we (i) compared parameters of visual attention between patients with MDD and healthy control participants, (ii) investigated the alertness-modulating effect of a single session of tDCS over the dlPFC on attention parameters in these groups, focussing on

alertness-dependent visual processing speed, and finally we (iii) tested the longevity of potential effects. Parameters of visual processing speed and further parameters of attention were quantified by applying TVA-based whole- and partial-report paradigms before, right after and 24 hours after tDCS treatment. Our main finding was a significant time point × stimulation interaction in MDD patients indicating that processing speed (as the only impaired baseline parameter) was exclusively enhanced in MDD patients 24 hours following a single session of verum, but not sham, anodal 2mA tDCS applied to the left dlPFC.

Attentional deficits at baseline assessment. At baseline, patients with MDD showed a significant visual perceptual slowing, as indicated by a processing speed that was 38% lower than that of healthy control participants. Our results go beyond previous publications and expand our knowledge of cognitive slowing in MDD patients: first, the theory-driven parametric approach delivers information on cognitively 'pure' mechanisms. It was reported previously that MDD patients perform slowly on attention-related tasks (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Lim et al., 2013; Paelecke-Habermann et al., 2005; Tsourtos, Thompson, & Stough, 2002). However, in such clinically established tasks multiple cognitive functions determine the overall performance and the contribution of these functions cannot be disentangled. By the use of the theory-driven parametric approach, we could demonstrate that, within the same letter report paradigms also used for demonstrating processing speed slowing, MDD patients did not show significant changes in vSTM storage capacity, minimal effective exposure duration or top-down control. These results, that are in line with the TVA model (Vangkilde, Coull, & Bundesen, 2012; Vangkilde, Petersen, & Bundesen, 2013) of alertness-related changes in processing speed and not in other attentional parameters, indicate that a reduced speed of visual information processing might be a core constraint in attentional processing in MDD. While the results need to be replicated in larger samples, at present state they imply that this slowing is not a secondary consequence of, for

example, limitations to short-term maintenance or from abnormal distractibility levels. Notably, such a basic impairment in processing speed will lead to below-average performance in all tasks that require speeded processing of multiple visual stimuli. Thus, it might well explain observed impairments in various tasks including those used to assess higher-order cognitive functions (e.g., Lim et al., 2013).

Second, the TVA-based assessment is not confounded with possible changes in motor performance. This is important since, in MDD patients, unspecific psychomotor effects that could result, for example, from pharmacological treatment, might affect response times in tasks that require fast motor performance. As the TVA-based assessment measures speed via report performance across different exposure durations, we can infer that slowing in processing speed parameter *C* indeed reflects cognitive (rather than unspecific motor) slowing.

Third, based on the neural TVA model (NTVA, Bundesen et al., 2005), an interpretation of perceptual slowing at the neuronal level is for the first time possible. The neural interpretation of TVA makes a specific link between the speed of visual categorization of an object and activations in the set of neurons that represent this object. That is, both the number of neurons representing object *x* and the activation level of the individual neurons representing object *x* are determinative of the speed at which the object is perceptually categorized. Thus, a strict TVA-based interpretation of our results is that MDD leads to a pathological reduction of the set of neurons that are allocated to the processing of visual information or to a decrease in the individual activation level of these neurons. This mechanistic description might be too simplified to account for complex processes on the brain network level. In more general terms, the close relationship between the TVA parameter visual processing speed to the concept of alertness, both theoretically (Bundesen et al., 2005) and empirically (e.g., Finke et al., 2010; Finke et al., 2012; Matthias et al., 2010;

Vangkilde et al., 2011), implies a pathologically low arousal resulting from functional connectivity changes in fronto-parietal alertness networks in MDD patients (Clemens et al., 2011; Coull et al., 1998; Sturm et al., 1999).

TDCS-induced changes: No immediate effects of tDCS in MDD patients or control participants. No significant effects were revealed directly following the application of verum compared to sham tDCS in the MDD patient or the healthy control group. These results are important, as they indicate that changes in resting state membrane potentials of neurons induced by tDCS over the dlPFC do not lead to immediate changes in processing speed. Thus, effects found later on cannot result from such unspecific arousal effects.

TDCS-induced changes: Significant improvement of visual processing speed in MDD patients in follow-up assessment. The significant time point × stimulation interaction in the MDD patient group indicated that, in the verum group, a significant enhancement of parameter processing speed *C* was found exclusively at the follow-up assessment, while no comparable effects were found in the sham group. These findings imply that even a single session of excitatory 2 mA tDCS over the left dlPFC leads to enduring modifications in fronto-parietal alertness networks on the brain level that in turn give rise to enhanced alertness-dependent processing speed on the neuro-cognitive level. In terms of the neurophysiological basis, this delayed effect on processing speed, observed 24 hours after the stimulation, is most likely not the result of immediate membrane polarization effects. Rather, the durable enhancement of processing speed could result from tDCS-induced NMDA-receptor-dependent plasticity effects (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003; Stagg & Nitsche, 2011). On a large-scale level, these after-effects may indicate tDCS-induced changes in the intrinsic fronto-parietal alertness network. Such functional connectivity changes might occur, and/or manifest in behavioural changes, with a certain delay following the stimulation (Keeser, Meindl, et al., 2011; Polanía, Paulus, Antal, &

Nitsche, 2011). Further tDCS studies which combine attention with resting state fMRI assessment could test these assumptions more directly.

A NTVA-based interpretation of our results implies that tDCS over the dlPFC reactivates the pathologically under-aroused processing system in MDD patients via mechanisms that lead to a higher number of neurons involved in processing visual information and/or that increase the excitability level of these neurons. Thus, the results imply that enhancement of prefrontal activity and/or modulation of functional connectivity within the compromised intrinsic alertness system of MDD patients by means of tDCS (Heller & Nitscke, 1997; Keeser, Meindl, et al., 2011; Posner & Petersen, 1990) triggers increased activation within the visual perceptual system when faced with visual target information. Given the overall relevance of intrinsic alertness to various tasks requiring fast information processing speed, our results imply benefits in daily life, and thus clinical behavioural relevance of brain activity and connectivity modulations induced by tDCS over the dlPFC. While there is previous evidence that single sessions of dlPFC tDCS can ameliorate unspecific cognitive deficits in MDD (Boggio et al., 2007; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013), we provide novel evidence for enduring beneficial effects – especially on the alertness-related visual processing speed.

To the best of our knowledge similar consolidating effects of single sessions of tDCS were so far only documented for stroke patients who showed improved attentional performance even for four weeks (Wilkinson et al., 2014). It is of course important to determine to what degree repetitive stimulation leads to more pronounced and enhanced longevity of the benefits. However, before testing attentional parameter changes in a more comprehensive, repetitive treatment study in MDD patients, it was important, as a proof of concept, to demonstrate that tDCS over the dlPFC does actually affect these parameters (Boggio, Asthana, Costa, Valasek, & Osorio, 2015).

We found differential effects of tDCS depending on the analysed attention parameter and participant group. First, tDCS influenced only the processing speed parameter *C* in MDD patients, whereas there was no indication of changes in the remaining TVA attention parameters. This is exactly the effect that was most likely to be expected since processing speed involves the function that should be modulated by activating the fronto-parietal alertness network. Furthermore, this is the function for which there is a possibility to ameliorate a deficit by means of tDCS which in turn should be reflected in an enhancing effect on the TVA parameter processing speed *C*, i.e., on the function showing a deficit. This implies that tDCS affects core deficits rather than improving performance on attention-related tasks indirectly via other modes of actions. Further, note that the only parameter enhanced by verum tDCS, processing speed *C*, was also the only parameter that differed between MDD patients and controls at baseline assessment. Second, we did not find a specific effect of verum tDCS in healthy control participants. Admittedly, they exhibited a better processing speed with increasing practice, however, the lacking interaction between time point and tDCS condition indicated that these slight practice effects did not differ between healthy control participants in the verum and sham condition. These results imply that effects of tDCS over the dlPFC critically depend on baseline performance level and might be restricted to low-performing participants, similar to cognitive enhancement effects of psychostimulant drugs (Finke et al., 2010; Müller, Steffenhagen, Regenthal, & Bublak, 2004). The neural underpinning of baseline and treatment response differences in MDD patients compared to healthy control participants might be a difference in baseline cortical activity. As baseline activity is considered to be a crucial tDCS response determinant (e.g., Jacobson et al., 2012), the likelihood of prefrontal tDCS to affect cognitive performance might be related to the initial degree of activation (and possibly connectivity) of the fronto-parietal system. Importantly, the relationship between arousal level and cognitive performance is assumed to

follow an inverted U-shape function, with a small range of optimal performance at medium arousal level (Yerkes & Dodson, 1908). Hence, in patients with MDD characterized by hypoactivated PFC areas (e.g., Baxter et al., 1989; Fitzgerald et al., 2008), tDCS might shift the degree of activation into the optimum range, while healthy participants with normal baseline arousal levels might not further benefit from tDCS-induced arousal increases.

Limitations. This study is limited by the fact that all patients were on antidepressant medication, implying that the effect of MDD on cognition as well as the tDCS effect could not be investigated independently of potential confounding medication effects. However, despite the concurrent intake of antidepressant medications, MDD patients demonstrated a specific cognitive impairment (i.e., reduced processing speed). In contrast, a medication-induced effect should be reflected in 'global' effects affecting all parameters. Moreover, in studies employing a repetitive stimulation protocol, therapeutic tDCS is typically applied add-on to antidepressant medications (Brunoni et al., 2016). Therefore, our result of tDCS-induced cognitive effects despite concurrent antidepressant medication, is highly relevant. Furthermore, four patients of the sham condition and two of the verum condition had the possibility to receive rescue medication with benzodiazepines (maximum 1.5 mg lorazepam equivalents, but no permanent treatment with benzodiazepines) during the study.

Moreover, the current sample size is rather small. Thus, replicating this study with a larger sample is necessary to further confirm the robustness of the results. The two study groups differed significantly with respect to education level. While our confirmatory analyses controlling for education influences replicated all our results, further testing with a strict matching procedure by recruiting patients who correspond to healthy controls with respect to every demographical variable is warranted. Our results support a functional contribution of the dlPFC to alertness-dependent visual processing speed. However, we cannot exclude that the beneficial effects attributed to anodal dlPFC stimulation are confounded by effects

induced by the cathode positioned on the right supraorbital region. To avoid these potential cathodal stimulation effects, an extracephalic electrode configuration could be considered alternatively but this would possibly also influence the cortical current flow (Wolkenstein & Plewnia, 2013). Finally, we did not evaluate more enduring stimulation after-effects, for example, one week post stimulation. Therefore, future studies should conduct long-term follow-ups to assess the stability of the effects going beyond 24 hours after stimulation.

Concluding remarks. The parametric assessment of attentional functions based on the TVA enabled us to tease apart the rather subtle effects of tDCS over the left dlPFC on different neuro-cognitive components. That is, in line with the known relevance of fronto-parietal networks to the state of alertness, we were able to identify a specific beneficial effect on TVA parameter visual processing speed *C*. As this effect was specific for the MDD patient group (and not found in healthy participants), processing speed enhancements following stimulation of left dlPFC seem to be more pronounced and might even be restricted to participants with low baseline activity in left fronto-parietal systems.

Taken together, by combining tDCS with TVA analysis in a partial- and whole-report paradigm in a sham-controlled, randomized, double-blind study, we were able to show (i) that MDD is associated with a significantly reduced rate of visual information uptake and, most critically, (ii) that activating the prefrontal alertness system by means of tDCS ameliorated this deficit. Our results suggest that even a single session of anodal tDCS over the dlPFC has relatively enduring effects – even going beyond the stimulation intervention – on an attention function depending on intrinsic alertness, and more specifically on visual processing speed.

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2.2 Study II: Parameter-based evaluation of attentional impairments in schizophrenia and their modulation by prefrontal transcranial direct current stimulation

In this paper, we report a double-blind, randomized, sham-controlled tDCS study that employed mathematical data modelling based on Bundesen's TVA in schizophrenia patients to assess (i) the specific attentional functions affected in schizophrenia patients compared to a healthy control group, (ii) the specific attentional benefits induced by a single session anodal tDCS over the left dlPFC, and (iii) the longevity of potential effects. Results revealed a significantly reduced visual processing speed and short-term memory storage capacity as primary sources of attentional deficits in schizophrenia. Furthermore, prefrontal tDCS interfered with (rather than enhanced) practice effects on visual processing speed in schizophrenia. This finding of a potential tDCS-induced disrupting effect on practice-dependent improvements in processing speed calls for further investigations and highlights the need for more neuroscience-based research in schizophrenia before tDCS can be broadly used as treatment option in all sectors of the healthcare system.

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2.2.1 Abstract

Attentional dysfunctions constitute core cognitive symptoms in schizophrenia, but the precise underlying neuro-cognitive mechanisms remain to be elucidated. In this randomized, double-blind, sham-controlled study, we applied, for the first time, a theoretically grounded modelling approach based on Bundesen's Theory of Visual Attention (TVA) to (i) identify specific visual attentional parameters affected in schizophrenia and (ii) assess, as a proof of concept, the potential of single-dose anodal transcranial direct current stimulation (tDCS; 20 minutes, 2 mA) to the left dorsolateral prefrontal cortex (dlPFC) to modulate these attentional parameters. To that end, attentional parameters were measured before (baseline), immediately after, and 24 hours after the tDCS intervention in 20 schizophrenia patients and 20 healthy controls. At baseline, analyses revealed significantly reduced visual processing speed and visual short-term memory storage capacity in schizophrenia. A significant stimulation condition × time point interaction in the schizophrenia patient group indicated improved processing speed at the follow-up session only in the sham condition (a practice effect), whereas performance remained stable across the three time points in patients receiving verum stimulation. In healthy controls, anodal tDCS did not result in a significant change in attentional performance. With regard to question (i) above, these findings are indicative of a processing speed and short-term memory deficit as primary sources of attentional deficits in schizophrenia. With regard to question (ii), the efficacy of single-dose anodal tDCS for improving (speed aspects of visual) cognition, it appears that prefrontal tDCS (at the settings used in the present study), rather than ameliorating the processing speed deficit in schizophrenia, actually may interfere with practice-dependent improvements in the rate of visual information uptake. Such potentially unexpected effects of tDCS ought to be taken into consideration when discussing its applicability in psychiatric populations.

2.2.2 Introduction

Visual attention dysfunctions, ranging from impairments in processing speed and visual short-term memory (vSTM) capacity to deficient top-down control (Dickinson, Ramsey, & Gold, 2007; Erickson et al., 2015; Forbes, Carrick, McIntosh, & Lawrie, 2009; Gold, Fuller, Robinson, Braun, & Luck, 2007; Johnson et al., 2013; Lee & Park, 2005), are commonly reported in schizophrenia and schizophrenia-spectrum disorders. However, the question of the precise neuro-cognitive mechanisms underlying the difficulties in attention tasks has not yet been resolved conclusively. For instance, it remains elusive whether both processing speed and working memory (WM) functions are affected in schizophrenia (Brebion, David, Jones, & Pilowsky, 2009) or whether slowed encoding processes are responsible for the reduced vSTM storage capacity in the respective attention tasks (Brebion, Amador, Smith, & Gorman, 1998; Dickinson et al., 2007; Rodriguez-Sanchez, Crespo-Facorro, Gonzalez-Blanch, Perez-Iglesias, & Vazquez-Barquero, 2007). Likewise, it is not clear whether the impaired encoding processes arise from impaired top-down controlled distractor inhibition (Barch & Ceaser, 2012; Erickson et al., 2014; Gold et al., 2006; Gold, Wilk, McMahon, Buchanan, & Luck, 2003; Hahn et al., 2010).

To determine whether these deficits can be attributed to losses of specific fundamental attention functions, a theoretically grounded modelling approach is required that can isolate and quantify (potentially compromised) core functions in an unconfounded measurement. Such an approach is provided by Bundesen's Theory of Visual Attention (TVA) (Bundesen, 1990), which already proved valuable for systematically characterizing cognitive deficits in diverse neuropsychiatric and neurological disorders (Finke, Bublak, Dose, Müller, & Schneider, 2006; Finke et al., 2011; Gögler et al., 2016). By combining this framework theory with simple psychophysical tests of whole- and partial-report of briefly presented letters, it is possible to derive independent estimates of parameters reflecting the individual

efficiency of core visual attention functions. Two of these parameters, visual processing speed, the rate of information uptake per second (*C*), and vSTM storage capacity, the maximum number of visual objects that can be represented at one time (*K*), capture general capacity aspects of the system; and the top-down control parameter (α) describes the system's (top-down) attentional selectivity. The ability of the TVA-based approach to provide 'process-pure' and independent measures of the various attention functions has been demonstrated in a range of studies revealing disorder-specific patterns of attentional deficits, for instance, selective impairment in only one parameter but not the others (Finke et al., 2006; Finke et al., 2011). Similarly, in healthy individuals, externally induced modulations of the alertness level have been shown to specifically increase processing speed, without influencing vSTM storage capacity (Finke et al., 2012). Furthermore, as the tasks do not require speeded responses, the parameters can be estimated uninfluenced by (e.g., antipsychotic drug-induced) motor side effects. Importantly also, unlike most standard neuro-cognitive tests, TVA-based assessment is highly sensitive so that even subtle deviations of cognitive performance from the norm can reliably be detected (Habekost & Bundesen, 2003). Given these advantages, the TVA-based approach is well suited for the prime purpose of the present study: to identify the specific attentional functions that are compromised in schizophrenia.

A secondary aim of this study was to investigate whether the compromised attentional performance in schizophrenia patients can be modulated by means of prefrontal transcranial direct current stimulation (tDCS). On a neuronal level, abnormal activation patterns within dorsolateral prefrontal cortex (dlPFC) attention networks are discussed as the underlying source of these attentional impairments (Barch et al., 2001; Barch & Ceaser, 2012; Cannon et al., 2005; Corbetta & Shulman, 2002; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Reichenberg & Harvey, 2007). Accordingly, modulation of intrinsic prefrontal networks

through tDCS has recently been proposed as potential non-invasive and safe treatment option for the remediation of cognitive dysfunctions in schizophrenia patients (Hoy & Fitzgerald, 2010; Mondino et al., 2014). TDCS modulates cortical excitability by passing small direct currents on to the scalp via electrodes with anodal and cathodal polarity. While short-term tDCS effects are attributed to tonic modulations of the resting membrane potential of cortical neurons affecting their firing rates, prolonged after-effects are presumed to be controlled by protein-synthesis dependent processes at the synaptic level (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003; Nitsche et al., 2004; Nitsche et al., 2005). Preliminary studies already provided promising results regarding the potential of tDCS to remediate cognitive deficits in psychiatric diseases, for example, in patients with major depression (Boggio et al., 2007; Gögler et al., 2016; Wolkenstein & Plewnia, 2013) or alcohol dependence (Nakamura-Palacios et al., 2012). However, with respect to schizophrenia, the available evidence is scarce and mixed (Hasan, Strube, Palm, & Wobrock, 2016; Mervis, Capizzi, Boroda, & MacDonald, 2017): one study applied 20 minutes of anodal tDCS with 2 mA to the left dlPFC and could not show that anodal tDCS improves performance on a procedural learning task in the whole sample, but still had a beneficial effect in a subgroup of patients (Vercammen et al., 2011). Another single-session experiment reported a positive effect of 2 mA anodal, but not 1 mA or sham, tDCS to the left dlPFC on a working memory task, 20 and 40 minutes after stimulation (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014). By contrast, in another study, a similar stimulation protocol was shown to be ineffective to influence cognitive functions measured by the MATRICS consensus cognitive battery composite score (Rassovsky et al., 2015). To expand our knowledge about the possible efficacy of tDCS in schizophrenia, in the second step of this proof-of-principle study, we explored whether the modulation of intrinsic networks through single-dose tDCS can have a functional significance for cognitive, and more specifically, visual attentional

processes in schizophrenia (Boggio, Asthana, Costa, Valasek, & Osorio, 2015). As anodal tDCS applied to the left dlPFC was previously shown to modulate intrinsic fronto-parietal networks in healthy humans, the beneficial cognitive effect of prefrontal tDCS has been attributed to an increase of the state of alertness (Keeser et al., 2011). Consequently, we hypothesized that prefrontal tDCS would influence particularly alertness-dependent cognitive processes, such as the speed by which visual stimuli are processed (Finke et al., 2010; Matthias et al., 2010; Vangkilde, Bundesen, & Coull, 2011). On the other hand, tDCS could also affect other attentional components such as vSTM storage capacity or attentional selectivity, subserved, at least partly, by prefrontal cortex and its functional and structural connections.

Measures assessing tDCS-induced benefits should be able to disentangle the potential effects on different attentional component processes subserved by prefrontal cortex (Barch & Ceaser, 2012; Cummings, 1993; Hoy et al., 2014; Rossi, Pessoa, Desimone, & Ungerleider, 2009). Furthermore, as the effects induced by single-dose tDCS are subtle (Berryhill, Peterson, Jones, & Stephens, 2014; Brunoni & Vanderhasselt, 2014), highly sensitive tools are a prerequisite for reliably detecting any (likely small) modulations of the various cognitive sub-processes. Previous studies using pharmacological interventions or cue stimuli have already revealed the high sensitivity of TVA parameters even to small manipulations of the alertness level (Finke et al., 2010; Finke et al., 2012; Matthias et al., 2010; Vangkilde et al., 2011). In this respect, TVA-based parametric attentional assessment provides, arguably, the best available tool for the aims of the present study, to (i) create a meaningful ‘attentional profile’ of schizophrenia patients and (ii) to examine for (subtle) tDCS-induced changes in attentional functions in these patients.

2.2.3 Methods

Participants

Twenty patients with a ICD-10 diagnosis of schizophrenia or schizophrenia-spectrum disorder (F20 = 19; F25 = 1), recruited from the Department of Psychiatry and Psychotherapy (LMU München), and the same 20, demographically matched, healthy controls that participated in our previous study (Gögler et al., 2016), were included in the investigation (see Table 1 and 2 for demographic and clinical data). The diagnoses, according to the WHO ICD-10 criteria for schizophrenia or schizophrenia-spectrum disorder, were made by two clinical psychiatrists of whom one (AH) is a member of this study group.

Patients were assessed for psychopathological symptoms [Positive and Negative Syndrome Scale PANSS; Calgary Depression Rating Scale for Schizophrenia (CDSS)] (Addington, Addington, & Schissel, 1990; Kay, Fiszbein, & Opler, 1987), disease severity [Clinical Global Impression Scale (CGI)] (Guy, 1976), and functioning [Global Assessment of Functioning Scale (GAF)] (American Psychiatric Association, 2013). The clinical rater (IP) was not involved in any other aspects of the study and had undergone extensive training in the use of the scales. Participants with a contraindication to tDCS were excluded. Further exclusion criteria were an IQ below 86 [German Multiple-Choice Vocabulary Test (MWT-B)] (Lehrl, Triebig, & Fischer, 1995), red-green colour blindness, and suicidal intent. All except one patient received second-generation antipsychotics and one patient received an additional first-generation antipsychotic medication. 68% of the patients received antipsychotic monotherapy. Furthermore, all patients were clinically stable as indicated by the PANSS values (see Table 2). Participants gave written informed consent and were monetarily compensated for their participation. The study conformed to the Declaration of Helsinki and was granted ethical approval by the LMU München Medical Faculty ethics committee. The study was registered at www.drks-neu.uniklinik-freiburg.de (identifier:

DRKS 00011665) and the WHO international clinical trials registry platform (http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00011665).

Table 1 Group Demographics.

	Schizophrenia Patients	**Healthy Controls**	***p***
Age	36.55 (9.16)	31.7 (8.31)	.09
Gender (m/f)	13/7	10/10	.34
Handedness (r/l/a)	18/1/1	18/2/0	.51
Education (years)	10.5 (1.57)	12.8 (.37)	.01
Verbal IQ (MWT-B)	106.88 (16.11)	112.2 (18.64)	.37

Note. Data are presented as means ± standard deviations or frequencies. MWT-B German Multiple-Choice Vocabulary Test; f female; m male; r right; l left; a ambidextrous. P-values refer to a statistical comparison between the schizophrenia patient and healthy control group.

Table 2 Comparison of Demographics and Clinical Ratings for Verum and Sham Groups.

	Schizophrenia Patients			**Healthy Controls**		
	Verum	**Sham**	***p***	**Verum**	**Sham**	***p***
Age	33.2 (7.67)	39.9 (9.65)	.54	30.8 (9.34)	32.6 (7.52)	.64
Gender (m/f)	4/6	3/7	.64	5/5	5/5	1.0
Handedness (r/l/a)	9/1/0	9/0/1	.37	9/1/0	9/1/0	1.0
Education (years)	10.8 (1.93)	10.2 (1.14)	.41	12.8 (.42)	12.9 (.32)	.56
MWT-B	110.62 (20.6)	103.13 (9.99)	.38	105.8 (14.48)	118.6 (20.81)	.13
Duration of illness (years)	7.15 (5.87)	6.56 (5.22)	.82	–	–	–
CDSS	5.9 (3.81)	4.5 (2.8)	.36	–	–	–
GAF	56.9 (8.17)	62.67 (5.29)	.09	–	–	–
CGI	4.2 (.63)	3.7 (.48)	.06	–	–	–
PANSS score						
Positive	13.4 (4.22)	12.0 (3.86)	.45	–	–	–
Negative	18.3 (3.89)	16.4 (6.19)	.42	–	–	–
General	31.4 (5.74)	29.0 (8.82)	.48	–	–	–
Total	63.1 (11.93)	57.4 (18.14)	.42	–	–	–
CPZ equivalents	437.5 (244.73)	443.47 (490.26)	.97	–	–	–
Antidepressants (y/n)	2/8	5/5	.35	–	–	–
Mood stabilizer (y/n)	1/9	0/10	1.0	–	–	–

Note. Data are presented as means ± standard deviations or frequencies. MWT-B German Multiple-Choice Vocabulary Test; CDSS Calgary Depression Rating Scale for

Schizophrenia; GAF Global Assessment of Functioning Scale; CGI Clinical Global Impression Scale; PANSS Positive and Negative Syndrome Scale; f female; m male; r right; l left; a ambidextrous; CPZ Chlorpromazine. P-values refer to a statistical comparison between verum and sham condition within the schizophrenia patient and healthy control group.

Study protocol

The experiment consisted of four sessions taking place on consecutive days at about the same daytime each. On day 1, participants were trained on the respective tasks of the TVA-based assessment. On day 2, a baseline TVA-based assessment was conducted (T0) and participants were randomly assigned to either the verum or the sham tDCS condition. On day 3, the TVA-based assessment (T1) took place straightaway after the tDCS (anodal or sham), and on day 4, a follow-up assessment of the attentional parameters (T2) was conducted to examine for the consolidation of potential tDCS after-effects (see Figure 1).

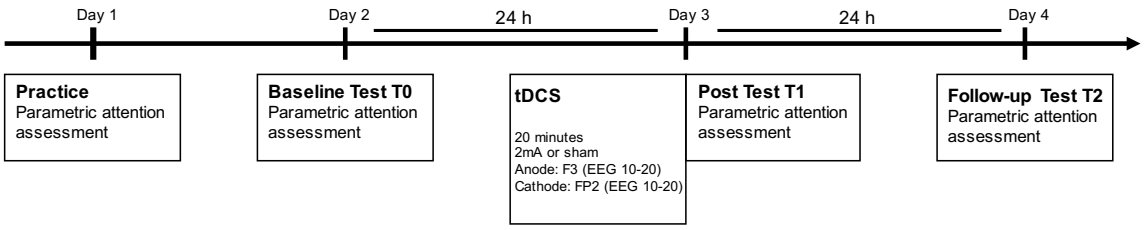

Figure 1 Flow-chart of the experiments.

Attentional assessment based on Bundesen's Theory of Visual Attention

Framework of the TVA approach

TVA is a comprehensive mathematical model of selective attention (Bundesen, 1990; Bundesen, Habekost, & Kyllingsbaek, 2005), which conceives of visual processing as a parallel competitive race of objects in the visual field for representation in a capacity-limited vSTM store (Desimone & Duncan, 1995): only those objects that are processed fastest will win the competition, that is, will be encoded in vSTM and thus become available for conscious report.

The speed with which an object in the display is processed depends on the attentional weight assigned to it. Both bottom-up and top-down factors, such as, respectively, stimulus saliency and fit with instructed (selection-relevant) target features, are crucial determinants of the magnitude of the attentional weight allocated to an object. Accordingly, only part of the objects will be represented within vSTM and can be used for further processing and goal-directed actions.

General method for TVA whole- and partial-report

Experiments took place in a dimly lit experimental laboratory at the Psychiatric Clinic of the Ludwig-Maximilians-Universität München (LMU Munich). TVA whole- and partial-report tasks were completed within one test session lasting about 1 hour; task order was counterbalanced across participants. Stimuli were presented on a 27-inch PC monitor on a black background, with a refresh rate of 100 Hz and a resolution of 1024 × 768 pixel. The viewing distance was set to approximately 60 cm. A trial started with the presentation of a white central fixation point (diameter: 1 cm) for 1000 ms which participants were instructed to fixate throughout the whole trial. After 250 ms, red and/or blue letters were briefly flashed on the display with exposure durations that were adjusted individually according to a criterion value in a pretest. The letters were randomly selected from a predefined set (ABCDEFGHJKLMNOPRSTUVWXZ), with a letter never appearing repeatedly in one trial. The stimuli display was either followed by an empty black screen or a pattern mask consisting of a blue-red scattered square (≈1.5° visual angle) visible for 500 ms at each stimulus location. The participant was instructed to report the letters in any order and without speed stressing. The experimenter typed the responses on a keyboard and then initialized the next trial. After each block, a visual performance feedback informed the participants about the amount of correctly named letters out of all reported ones (in %). To avoid too

conservative and too liberal responses, participants should aim for correctness between 70–90%.

TVA-based whole-report. On each trial six letters, either all red or blue, appeared on an imaginary circle with a radius of 6 cm (5.73° of visual angle) around the fixation point (see Figure 2). Participants had to identify and report as many letters as possible.

To find the five adequate exposure durations for a given participant a pretest of four blocks à 12 trials was conducted prior to the main whole-report task in each test session. Three types of trials were used in this pretest: two 'easy' trials (i.e., one longer and one unmasked trial) and one adjusting trial in which initially, the six letters were flashed for 80 ms. If the participant could correctly identify at least one letter, exposure durations were decreased in steps of 10 ms until the lowest individual threshold, for which no letter could be reported anymore, was detected. This threshold was used to find an adequate set of four additional, longer exposure durations for the subsequent whole-report task (e.g., 10, 20, 40, 90, and 200 ms). In these five conditions letters were masked. Additionally, in two unmasked conditions, letters were presented in the second shortest and the longest exposure duration condition. Consequently, there were seven 'effective' exposure duration conditions. In unmasked trials an afterimage of the display emerges which extends the effective exposure durations by a constant duration which is defined by parameter μ (given in ms) (Sperling, 1960). The patient group's average minimum exposure duration was 21 ms (SD = 4.47 ms) and did not differ significantly ($t(38) = -1.1$, $p = .32$) from that of the control group, which was on average 20 ms (SD = 0 ms).

In total, the whole-report task consisted of 140 trials, separated into 4 blocks of 35 trials. Within each block, each display condition was presented equally often in randomized order. Based on the performance in the whole report task, the individual processing capacity aspects reflected by the TVA parameters perceptual processing speed C and vSTM capacity

K, can be estimated by mathematical data modelling (Kyllingsbæk, 2006). The probability of stimulus identification is modelled by an exponential growth function, relating the mean number of reported objects to the exposure duration. The use of seven effective exposure durations allows a broad depiction of the performance spectrum including early and late aspects of participant's whole-report functions, and consequently a reliable model fit of the data. The growth parameter reveals the rate at which stimuli are processed (measured in visual elements per second; *C*), and the asymptote specifies the maximum number of objects that can be represented within vSTM store (*K*) (see Figure 3). Two further parameters, *minimum* effective exposure duration t_0 and effective *additional* exposure duration in unmasked displays μ, were also estimated (and did not differ significantly between groups and were not modulated by tDCS). These parameters merely serve the valid estimation of the parameters of interest but apart from this, they were of no further relevance in the present study.

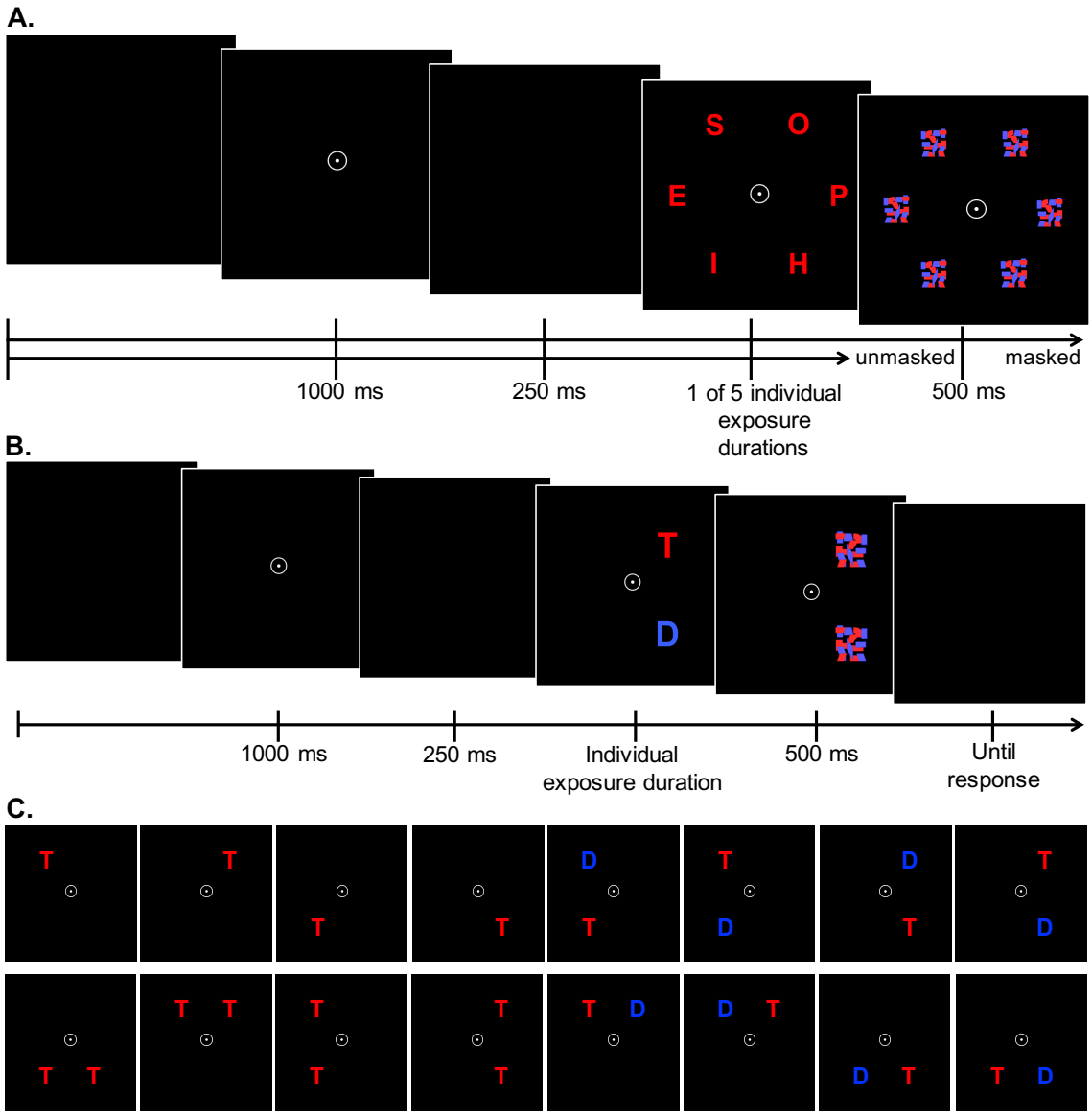

Figure 2 (A) Theory of Visual Attention (TVA) whole-report task procedure. After the presentation of a central fixation circle for 1000 ms and a brief delay of 250 ms, six letters are flashed in an imaginary circle either in red or blue font for one of five individually adjusted exposure durations (identified in a pretest). In these five exposure duration conditions letters were masked for 500 ms. In two unmasked conditions, letters were presented in the second shortest and the longest exposure duration condition. (B) Trial sequence and (C) display types of TVA partial-report task. After the presentation of a central fixation circle for 1000 ms and a brief delay of 250 ms, one of the 16 possible display types appears for a predetermined individual exposure duration. Following that, presented stimuli (T = target = red letters; D = distractor = blue letters) are masked for 500 ms.

TVA-based partial-report. On each trial either one or two letters (1 target, 2 targets or a target plus distractor) were flashed in the corners of an imaginary square (located 7.5 cm around the fixation point). If two letters were presented on the display, they either appeared in a row or in a column, but never diagonally. Participants had to report target letters (in red colour) only, whilst ignoring distractors (blue). The stimulus arrays (see Figure 2B) appeared in randomized order and stimuli were always masked for 500 ms. The partial-report task consisted of sixteen conditions (4 single-target T, 8 target plus distractor T-D, 4 dual-target conditions T-T), which were counterbalanced across all six blocks (see Figure 2C). A pretest (2 blocks of 24 trials) was used to determine the individual exposure durations of the presented letter(s): first, letters were displayed with an initial exposure duration of 80 ms. If participants could identify two letters in the dual-target condition, exposure duration was decreased by steps of 10 ms until they could name, on average, one letter per trial correctly, whereas the exposure duration was increased by steps of 10 ms if they could not identify any letter. Exposure duration was kept unchanged, if they could identify one of the two target letters. Next, performance at the determined exposure duration was verified for the different experimental conditions in another turn of 24 trials. An adequate performance is denoted by correctly reported letters of 70–90 % for single target conditions (T) and at least 50 % for dual-target conditions. Otherwise exposure durations were in- or decreased manually by the experimenter and performance was rechecked in another turn of 24 trials. The patient group's average exposure duration was 81.5 ms (SD = 32.85) and did not differ significantly ($t(38)$ = .95, p = .38) from those of the control group, that was on average 75.33 ms (SD = 27.69). The partial-report task consisted of 288 trials separated into 6 blocks of 48 trials. From the probability of stimulus identification, attentional weights are derived for targets (w_T) and distractors (w_D). Parameter α is defined as the ratio of distractor to target weights (w_D/w_T) and reflects top-down efficacy, i.e., the ability to prioritize task-relevant over task-irrelevant

information. Values of α close to zero indicate a high selectivity, i.e., targets receive more weight than distractors. Values of α close to one signify no selection and values larger than one imply that distractors receive more weight than targets, and hence were seen more easily.

Transcranial direct current stimulation

TDCS was delivered by a CE-certified stimulator (neuroConn, Germany) through saline-soaked surface sponge electrodes (35 cm^2) at 2 mA for 20 minutes (plus 15 seconds fade-in and fade-out). The anode was placed above the left dlPFC located via F3 (EEG 10-20 system). This position covers Brodmann areas 8, 9 or 46 on the medial frontal gyrus – areas representative of the left dlPFC (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003; Homan, Herman, & Purdy, 1987). The cathode was placed above the right supraorbital area (FP2). This is the standard electrode montage used in physiological studies (Nitsche & Paulus, 2011), and also in behavioural studies, this electrode montage was reported to modulate cognition both in healthy humans and patients (Boggio et al., 2007; Hoy et al., 2014; Keeser et al., 2011).

Based on previous publications, sham stimulation was performed in the same way as verum stimulation, but the current was applied only for 30 seconds (plus 15 seconds fade-in and fade-out) (Gandiga, Hummel, & Cohen, 2006; Poreisz, Boros, Antal, & Paulus, 2007). Participants were randomly assigned to verum or sham tDCS by a computer-generated randomization list (https://www.random.org/lists/). To ensure double-blindness of both participants and experimenter, the experimenter did not have access to this list during the study; moreover, tDCS was performed by investigators not otherwise involved in the examination of patients. Ten patients received verum left-anodal tDCS, and the remaining 10 patients underwent sham tDCS. Similarly, 10 healthy control participants received verum tDCS and 10 healthy controls received sham tDCS. During the stimulation, participants were

not performing any task. This 'offline' protocol was chosen as we were mainly interested in tDCS after-effects on attentional functions – both immediate and longer lasting ones of potential clinical relevance. Potential tDCS-induced adverse effects were examined by a post-hoc comfort rating scale filled in by the participants (Palm et al., 2014).

Data analysis

Data were analysed using IBM SPSS 22. The alpha level was set to .05. Baseline group differences in demographic and clinical variables were analysed using independent t-tests for continuous variables and χ^2-tests or, where appropriate, Fisher's exact tests, for categorical variables. Baseline group differences in attentional performance as well as baseline differences in attentional performance, demographic and clinical characteristics (patients) in participants assigned to the verum versus sham tDCS conditions within these two groups were analysed by independent t-tests. Cohen's *d* was calculated as a measure of the effect size for the group differences in attentional performance (Cohen, 1988). To assess immediate and enduring effects of tDCS on the attentional parameters, two-way mixed ANOVAs were performed with time point (T0, T1, T2) as within-subject factor and stimulation condition (verum vs. sham tDCS) as between-subjects factor, separately for the healthy control and the schizophrenia patient group. Mauchly's test of sphericity was used to test the assumption of sphericity and, if significant, we applied Huyn-Feldt correction. In case of a significant interaction, the data was tested for simple main effects of time point, that is, we assessed differences in attentional parameters between time points for each level of the between-subjects factor stimulation condition.

By means of χ^2-tests, we assessed whether the number of participants who believed to have received verum stimulation differed between the verum and sham conditions. Furthermore, comfort ratings were compared between participants of the verum and sham

conditions through independent t-tests.

2.2.4 Results

All schizophrenia patients and healthy control participants completed the entire experiment. No unexpected adverse effects of tDCS, such as skin burns, pain or headache, were reported or revealed by the comfort rating questionnaire.

Demographic and clinical characteristics

The schizophrenia patient and healthy control groups were matched according to age ($p = .09$), gender ($p = .34$), IQ ($p = .37$), and handedness ($p = .51$). The two groups differed significantly with respect to education level ($p < .01$). In both groups, participants receiving verum and sham stimulation did not differ significantly with respect to any of the demographic and clinical characteristics (all ps $\geq .06$; Table 2).

Baseline task performance – healthy control versus schizophrenia patient group

Whole-report results

In Figure 3, the mean number of correct reports as a function of the (effective) exposure duration is depicted for one representative schizophrenia patient and one healthy control participant. The curves represent the maximum likelihood fits to the observed data, which correlated fairly well. TVA's best fits accounted for $r^2 = 92\%$ of the variance of the observed mean scores at the different exposure durations. Based on mathematical data modelling of the performance (correct letter reports) in the whole-report task (Kyllingsbæk, 2006), individual estimates were derived for perceptual processing speed *C* and vSTM storage capacity *K*. Table 3 depicts all means and standard deviations of the respective baseline TVA parameters in the healthy controls and schizophrenia patients.

Perceptual processing speed *C*. Analysis revealed processing speed to be significantly lower in schizophrenia patients ($M = 29.55$ items/second, $SD = 21.22$) than in

healthy controls (M = 43.86 items/second, SD = 19.18; $t(38) = 2.24$, $p = .03$; see Figure 4). This effect is also illustrated by the slope of the whole-report functions depicted in Figure 3, which is steeper for the representative control participant than for the schizophrenia patient. Thus, the rate of visual information uptake within a given unit of time is significantly reduced in schizophrenia. Computation of Cohen's d yielded a medium to large effect size ($d = .7$) and a 43% non-overlap of the two distributions of C scores.

Visual short-term memory capacity *K*. Analysis disclosed vSTM storage capacity to be significantly decreased in schizophrenia patients (M = 3.01, SD = 0.78 items) compared to healthy controls (M = 3.67, SD = 0.94 items; $t(38) = 2.\ 42$, $p = .02$; see Figure 4). As can be seen from Figure 3, as exposure duration increases, report performance approaches an asymptotic level, which represents the (depicted individuals') vSTM storage capacity: the patient's asymptote is lower than that of the healthy control participant – illustrating that the mean number of items that can be represented in vSTM is reduced in schizophrenia. The effect size is large ($d = .8$), with a 47.4% non-overlap of the two distributions of K scores.

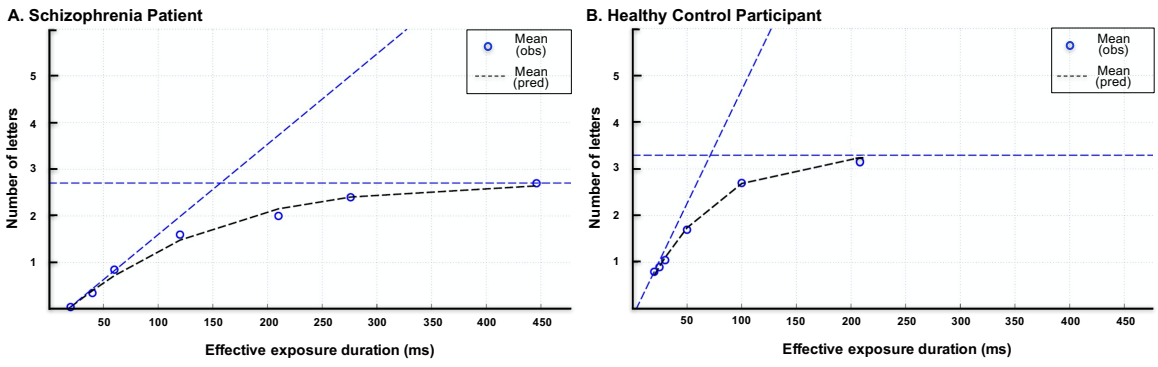

Figure 3 Whole-report performance of a representative schizophrenia patient (A) and a healthy control participant (B). Mean number of correct letter reports as a function of exposure duration. Circles represent observed values (= obs), dashed lines represent the best fits of the observed scores by the applied model (pred = predicted). The estimate of visual short-term memory capacity K and processing speed C is indicated by the horizontal and diagonal dashed lines, respectively.

Table 3 TVA Whole- and Partial-Report Parameters at Baseline for the Schizophrenia Patient and Healthy Control Group.

	Schizophrenia Patients		Healthy Controls		
	M	***SD***	***M***	***SD***	***p***
C	29.55	21.21	43.86	19.18	.03
K	3.01	.78	3.67	.94	.02
α	.35	.18	.36	.22	.93

Note. *C*: Visual perceptual processing speed (elements/sec); *K*: Visual short-term memory capacity (number of elements); *α*: efficiency of top-down control. P-values refer to a statistical comparison between the schizophrenia patient and healthy control group.

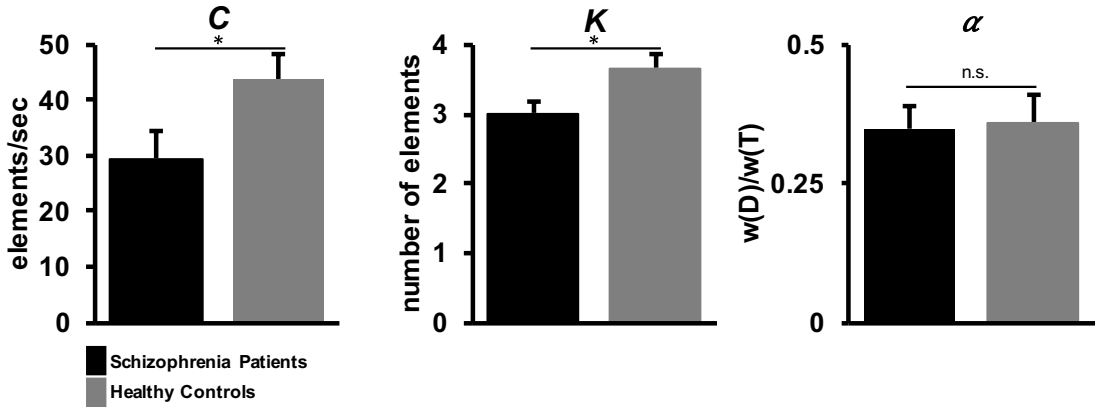

Figure 4 Whole- and partial-report results. Mean estimates and standard errors for the TVA parameters processing speed *C*, short-term memory capacity *K* and efficiency of top-down control *α*.

Partial-report results

Mathematical modelling of performance in the partial-report task permits inferences to be drawn about the functioning of attentional selectivity, reflected in the top-down control parameter *α* (Kyllingsbæk, 2006). There was again a close correspondence between the observed performance at the different exposure durations and TVA's best fits to the data: the predicted values accounted for $r^2 = 91\%$ of the variance of the observed mean scores.

Top-down control *α*. Analysis revealed statistically comparable estimates of top-

down control α between schizophrenia patients (M = .35, SD = .18) and healthy controls (M = .36, SD = .22; $t(38)$ = .09, p = .93; see Figure 4).

Immediate and enduring effects of tDCS on attentional parameters

Healthy controls

For processing speed C, the ANOVA revealed the main effect of time point to be significant: processing speed increased from baseline to post and then to follow-up test ($F(2, 36)$ = 4.05, p = .03; see Figure 5). No other significant effects were obtained (all ps ≥ .12; for means and standard deviations, see Table 4). As these are the results of our in-house, 'historical healthy-control cohort', we refer to Gögler et al. (2016) for a more detailed description of the findings.

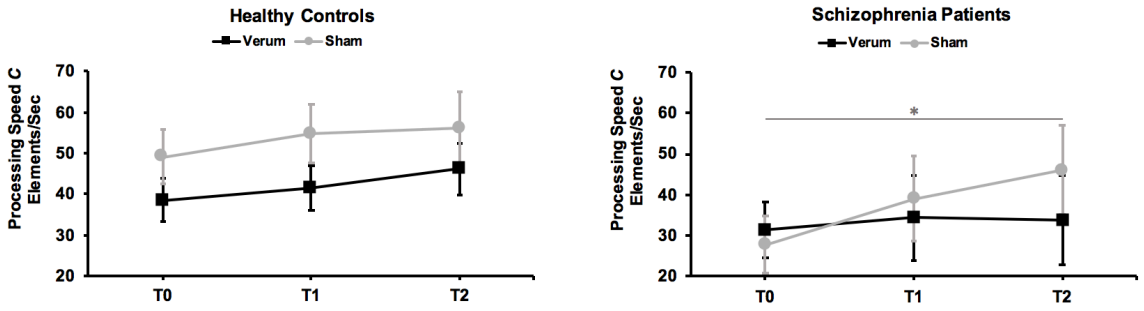

Figure 5 Effects of tDCS on mean perceptual processing speed C in healthy controls and schizophrenia patients. Processing speed was assessed at baseline (T0), directly after tDCS (T1) and 24 hours after tDCS (T2).
Error bars represent standard errors of the means, * p < .05.

Table 4 TVA Whole-and Partial-Report Parameters in the Healthy Control and Schizophrenia Patient Groups for the Three Time Points (T0, T1, T2).

		T0		T1		T2	
	tDCS condition	***M***	***SD***	***M***	***SD***	***M***	***SD***
Healthy controls							
C	Verum	38.59	16.76	41.53	17.11	46.18	19.92
	Sham	49.13	20.84	54.69	22.49	56.09	28.29
K	Verum	3.47	.82	3.33	.84	3.48	.78
	Sham	3.88	1.04	3.86	.93	4.01	1.02
α	Verum	.27	.20	.22	.26	.33	.16
	Sham	.45	.21	.42	.20	.39	.11
Schizophrenia patients							
C	Verum	31.36	16.83	34.33	19.02	33.92	19.01
	Sham	27.73	25.69	39.02	41.92	46.01	44.91
K	Verum	3.40	.64	3.47	.59	3.64	.64
	Sham	2.63	.75	3.06	.69	3.03	.59
α	Verum	.36	.15	.40	.17	.42	.27
	Sham	.34	.21	.38	.18	.36	.13

Note. *C*: Visual perceptual processing speed (elements/sec); *K*: Visual short-term memory capacity (number of elements); *α*: efficiency of top-down control.

Schizophrenia patients

Baseline comparisons between verum and sham condition. For the schizophrenia patients, analyses revealed no significant baseline differences between the verum and sham tDCS conditions for the TVA parameters processing speed *C* and top-down control *α* (all *t*s ≤ .37, all *p*s ≥ .30). However, there was a significant difference with respect to parameter *K*: patients in the verum condition exhibited a significantly higher vSTM capacity ($M = 3.39$, $SD = .64$ items) than patients in the sham condition ($M = 2.63$, $SD = .75$ items; $t(18) = 2.44$, $p = .03$). See Table 4 for respective means and standard deviations.

TDCS effects on whole-report performance. For processing speed, analysis revealed a significant main effect of time point ($F(2, 36) = 6.72$, $p = .01$) and a significant interaction between tDCS condition and time point ($F(1.64, 29.44) = 3.67$, $p = .04$) in the patient group. Separate ANOVAs computed for the two tDCS conditions (to follow up the

interaction) revealed the effect of time point to be significant for the sham group ($F(1.41, 12.67) = 6.48$, $p = .02$): processing speed C increased somewhat from the baseline ($M = 27.73$, $SD = 25.69$ items/second) to the post test ($M = 39.02$, $SD = 41.92$ items/second), yielding a trend-level difference ($t(9) = –2.04$, $p = .07$); and there was a further increase to the follow-up test, manifesting in a statistically reliable difference between the baseline and follow-up tests ($M = 46.01$, $SD = 44.91$ items/second; $t(9) = –2.87$, $p = .02$; see Figure 5). On average, patients receiving sham stimulation could process some 18 elements/second (67%) more at the follow-up compared to the baseline test. A Cohen's d of .50 indicated a medium effect size. In contrast to the sham group, there was no main effect of time point for the verum group, ($F(2, 18) = .69$, $p = .51$), that is, processing speed C remained stable across the various time points of testing. At the single-subject level, only a single patient (out of ten) in the verum condition showed an increase in the parameter processing speed C from baseline to follow-up testing considering a threshold of ≥ 50% improvement. In contrast, seven out of ten patients in the sham condition showed an increase in processing speed (≥ 50%) from baseline to follow-up testing. A Fisher's Exact test between tDCS condition (sham/verum) and 'improvement ≥ 50%' (yes/no) yielded a significant association between tDCS condition and 'improvement', $p = .02$.

For the parameter vSTM storage capacity K, analysis yielded a significant main effect of time point ($F(2, 36) = 4.87$, $p = .01$): the patients' ability to represent items in vSTM increased from baseline to post and further to follow-up test. However, the time point × tDCS condition interaction was not significant ($F(2, 36) = 1.36$, $p = .27$).

TDCS effects on partial-report performance. For the parameter top-down control α, analysis yielded no statistically reliable effects (all ps ≥ .56). We repeated these analyses using 'GAF' and 'CGI' as covariates, which confirmed the results for all three parameters, and therefore indicate that the observed tDCS effect in the schizophrenia patient group cannot

be explained by differences in these clinical characteristics between the verum and sham condition.

Integrity of blinding and comfort rating

Participants were successfully blinded: of the schizophrenia patients, nine patients in the verum and seven in the sham condition indicated that they had received verum stimulation ($\chi^2(1) = 1.25$, $p = .26$). Of the healthy controls, seven participants in the verum and three in the sham condition believed that they had received verum stimulation ($\chi^2(1) = 3.20$, $p = .07$). Within both the schizophrenia patient and the healthy control group, there were no significant differences between participants in the verum and sham conditions with respect to comfort ratings (sum score of the 10-point Likert scales) relating to the time during and after the stimulation (all ts ≤ 2.01, all ps $\geq .06$).

2.2.5 Discussion

The present study had two objectives. First, we applied mathematical data modelling based on Bundesen's TVA to isolate the particular attentional deficits in schizophrenia patients compared to healthy controls. Second, we assessed whether these deficits could be modulated by means of a single, 20-minutes tDCS session with 2 mA over the dlPFC. In brief, we found an altered pattern of attentional parameters, expressed by significantly reduced visual processing speed *C* and vSTM storage capacity *K*. However, contrary to our hypothesis, we did not find evidence that verum tDCS, compared to sham stimulation, would improve attentional functioning. Instead, a differential development from baseline to follow-up assessment indicated that the normal, practice-dependent increase in visual processing speed that occurs with repeated application of the whole-report task (shown by healthy controls and

patients in the sham group) disappears when verum tDCS is applied to the left dlPFC in schizophrenia patients.

Visual perceptual slowing and vSTM capacity deficit at baseline assessment. To our knowledge, this is the first study applying TVA-based parametric attentional assessment in schizophrenia patients. This enabled us to isolate an impairment of general attentional capacity (without an impairment of attentional selectivity) as the primary factor compromising visual attentional functioning in schizophrenia. Specifically, at baseline, schizophrenia patients exhibited significantly reduced visual processing speed *C* and vSTM storage capacity *K*. The neural interpretation of the TVA (NTVA) (Bundesen et al., 2005) attributes processing speed changes to changes in either the activation level or the overall number of the neurons that are devoted to processing the visual information presented. On this notion, our results imply that schizophrenia leads to a reduced overall arousal level of the brain, likely owing to changes in the excitability of the alertness network. NTVA furthermore assumes that vSTM storage relies on a cortical-thalamic circuitry supporting activity in reverberating loops. Accordingly, our finding of schizophrenia patients exhibiting a reduction in the amount of information they can maintain in vSTM would imply that the functional integrity of this system is impaired.

From a general point of view, our findings are in line with previous reports of processing speed and vSTM deficits in schizophrenia revealed by means of various other testing procedures (Erickson et al., 2015; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Nuechterlein et al., 2004; Perlstein, Carter, Noll, & Cohen, 2001). They also replicate high effect sizes for differences in vSTM storage capacity estimates between schizophrenia patients and healthy controls based on experimental measures (Gold et al., 2010; Gold et al., 2003; Johnson et al., 2013). However, using the TVA approach, which is based on a well-grounded computational theory, we could assess relevant and distinct attentional components of interest

in an independent manner – without confounding speed of information uptake, vSTM capacity, and distractibility (Bublak et al., 2005; Finke et al., 2005; Vangkilde et al., 2011). Extracting these components within the same tasks with identical stimuli and response requirements revealed an attentional profile specific for schizophrenia. As selectivity aspects of attention were not significantly altered in schizophrenia patients compared to healthy controls, we can rule out that the capacity limitations are secondary consequences of impaired top-down control. This is again in line with previous reports of preserved attentional control of information encoding into short-term memory (Gold et al., 2006). Note that the present results have no bearing with regard to top-down controlled processing in situations with (bottom-up) highly salient distractors. There is evidence that patients with schizophrenia exhibit deficits in attentional selection when salient distractors compete for attentional selection (Hahn et al., 2010). Furthermore, our results are unlikely attributable to unspecific antipsychotic drug-induced motor side-effects, as the TVA-based assessment requires only unspeeded verbal responses. Similarly, these visual attentional deficits are unlikely attributable to eye movement impairments, often reported in schizophrenia patients (e.g., Levy et al, 2010), as the TVA-based assessment uses very brief exposure durations below the latency of saccadic eye movements. Besides, eye movement abnormalities should be reflected in elevated perceptual thresholds (parameter t_0). However, this parameter was found to be not significantly different between patients and healthy controls. The latter also implies that motivational impairments unlikely underlie the observed visual attentional deficits.

TDCS-based modulation of attentional parameters. Unexpectedly, we found a significant increase in the (impaired) parameter processing speed *C* at the follow-up assessment only in patients receiving sham (but not verum) tDCS. That is, single-session verum tDCS over the dlPFC appears to be ineffective, or maybe even harmful, for improving attentional functioning in schizophrenia – a finding that echoes those of a recent study (Palm

et al., 2016) which assessed the effect of two-week dlPFC tDCS on the secondary outcomes WM (SOPT), processing speed (TMT-A), and executive functioning (TMT-B) in schizophrenia patients with predominantly negative symptoms. In contrast, in the present study, tDCS did not influence information uptake processes in healthy control participants. This differential effect of tDCS on the processing speed parameter *C* in healthy participants and in those suffering from schizophrenia may be explained by unexpected effects of tDCS in schizophrenia. Schizophrenia is a disorder of disturbed neuronal plasticity with alterations in glutamatergic neurotransmission (Hasan et al. 2013), is characterized by a dysfunction in interneurons and GABAergic neurotransmission affecting microcircuity (Benes et al. 2015) and a dopaminergic dysbalance is evident (Howes and Kapur, 2008). TDCS effects are dependent on NMDA, GABA and dopaminergic receptor activity (Ziemann et al. 2015) and have been discussed not only to act at the soma of pyramidal neurons, but possibly also on the interneuron level (Jackson et al. 2016). Due to these alterations that are all related to the mode of action of tDCS, one could speculate that tDCS may have unexpected clinical and neurophysiological effects in schizophrenia patients.

Two potential mechanisms, which cannot be differentiated based on our study, might be responsible for the reduction in processing speed increase from baseline to follow-up testing. First, given that we observed practice-dependent enhancement of visual processing speed from baseline to follow-up assessment in healthy participants in both the sham and the verum group and in schizophrenia patients in the sham group, the application of tDCS in schizophrenia patients might interfere with practice effects that likely rely on implicit procedural learning of performing the whole-report task. Alternatively, tDCS might impact processing speed by reducing the overall arousal level in schizophrenia patients' brains for at least 24 hours. Thus, for patients in the verum group, even though they received the same amount of whole-report training as the sham group, the training benefits are effectively

nulled by the lowered arousal level. The present results highlight the need for further safety assessments in tDCS studies involving psychiatric patients and, more particularly, for more systematic evaluation of tDCS effects on cognition before embarking on large-scale clinical trials.

Our results suggest that the applied stimulation parameters – tDCS for 20 minutes at 2 mA over the left dlPFC – are not appropriate for ameliorating attentional dysfunctions (as assessed by TVA) in schizophrenia patients. This appears to be at odds with other studies that used similar tDCS protocols and reported beneficial effects in reducing negative symptoms and improving cognitive functions in schizophrenia (Hoy et al., 2014; Palm et al., 2016) and other psychiatric disorders (Boggio et al., 2007). Reasons for the unfavourable effects on cognition obtained in the present study might be the relatively high intensity and duration of the stimulation. Although these settings are typical for the field of cognitive neuroscience, they have yielded unexpected effects in previous tDCS studies of motor cortex, where nonlinear effects of dosage have been reported with healthy participants: greater tDCS intensity, rather than being associated with higher efficacy of stimulation, shifted the excitability alterations (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). Moreover, the individual response variability of tDCS at both 1 mA and 2 mA (Lopez-Alonso, Fernandez-Del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015; Strube et al., 2016; Wiethoff, Hamada, & Rothwell, 2014) may hamper the efficacy of our intervention in the given population offering an alternative explanation of the here reported unexpected findings. As the positioning of the electrodes can impact tDCS effects (Nitsche & Paulus, 2000), our negative finding might also have been the result of non-optimal electrode montage: it cannot be ruled out that the ‘reference’ electrode over the right supraorbital area induced confounding effects and that, for instance, larger (being less active) or extracephalic reference electrodes might have produced a different outcome. Likewise, although in imaging

studies this kind of electrode configuration was shown to modulate fronto-parietal attention networks (Keeser et al., 2011), the position of the 'active' electrode above the left dlPFC might have been inappropriate for modulating visual attentional functions in schizophrenia patients. Finally, it should be borne in mind that schizophrenia patients exhibit significant alterations in dopaminergic transmission and that all antipsychotics act on dopamine receptors. In this context, dopaminergic modulation has been shown to impact the efficacy of tDCS in a non-linear manner, resulting, for example, in a reversal of plasticity effects (Agarwal et al., 2016; Monte-Silva et al., 2009).

Limitations. First, the sample size of this proof-of-concept study, while being comparable with other studies in the field, was relatively small, increasing the probability of a type II error. Therefore, findings must be confirmed in a larger sample before generalizing these results. The limited sample size and the use of a between-subjects design may limit our findings. Albeit not likely, as the groups were comparable with respect to the initial visual processing speed parameter, it cannot be excluded that the observed effect may be explained in partly by differences in clinical and sociodemographic characteristics between both conditions. Moreover, as all patients received antipsychotic medication, the effect of tDCS on our cognitive parameters could not be investigated independently of potential confounding medication effects. However, Pearson correlations between CPZ and cognitive performance (C, K, α) at study inclusion did not correlate significantly (C: r = .37, p = .11; K: r = .44, p = .18; α: r = .41, p = .08), indicating that antipsychotic doses had no impact on our outcome variables. Regarding tDCS effects, we cannot rule out that these may have resulted from interactions between medication and tDCS yielding the unfavourable outcome. As outlined above, antipsychotic drug-induced dopaminergic modulations can affect tDCS-induced changes in cortical excitability and plasticity (Agarwal et al., 2016; Monte-Silva et al., 2009). However, as tDCS is considered an add-on treatment option, experimental trials with

medicated patients would, arguably, be representative for a clinical setting.

Conclusions. In the present study, employing TVA-based parametric assessment of attentional functions, schizophrenia patients were revealed to exhibit a characteristic pattern of attentional capacity impairments: a significantly reduced rate of visual information uptake (per time unit) and a significantly reduced vSTM storage capacity (in terms of the number of items that can be maintained simultaneously). Combining this approach with a tDCS intervention revealed that 20 minutes of 2 mA prefrontal tDCS interferes with (rather than enhances) practice effects on visual processing speed in schizophrenia. This finding of a potential tDCS-induced disrupting effect on the here investigated cognitive domain calls for further investigation and highlights the need for more neuroscience-based research in schizophrenia.

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2.3 Study III: Object integration requires attention: Visual search for Kanizsa figures in parietal extinction

In this paper, we report a study that investigates the interaction between object integration processes (i.e., perceptual grouping) and attentional selection mechanisms. For this purpose, we tested a group of extinction patients suffering from a lateral bias of spatial attention and a group of healthy controls in a visual search paradigm that presented to-be grouped nontarget and target Kanizsa figures. Results revealed generally comparable search performance in both patients and controls, and evidence for preserved grouping in displays with single objects. By contrast, an extinction-specific spatial bias emerged in the patients particularly when confronted with a competitive search situation that presented multiple to-be-grouped items. From this pattern of results, we conclude that perceptual grouping crucially depends on the degree of competition among visual input. Together, our results indicate that object integration requires attention, thus challenging accounts according to which pre-attentive processing suffices to represent complete objects.

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2.3.1 Abstract

The contribution of selective attention to object integration is a topic of debate: integration of parts into coherent wholes, such as in Kanizsa figures, is thought to arise either from pre-attentive, automatic coding processes or from higher-order processes involving selective attention. Previous studies have attempted to examine the role of selective attention in object integration either by employing visual search paradigms or by studying patients with unilateral deficits in selective attention. Here, we combined these two approaches to investigate object integration in visual search in a group of five patients with left-sided parietal extinction. Our search paradigm was designed to assess the effect of left- and right-grouped nontargets on detecting a Kanizsa target square. The results revealed comparable reaction time (RT) performance in patients and controls when they were presented with displays consisting of a single to-be-grouped item that had to be classified as target vs. nontarget. However, when display size increased to two items, patients showed an extinction-specific pattern of enhanced RT costs for nontargets that induced a partial shape grouping on the right, i.e., in the attended hemifield (relative to the ungrouped baseline). Together, these findings demonstrate a competitive advantage for right-grouped objects, which in turn indicates that in parietal extinction, attentional competition between objects particularly limits integration processes in the contralesional, i.e., left hemifield. These findings imply a crucial contribution of selective attentional resources to visual object integration.

2.3.2 Introduction

Visual scenes are typically cluttered, containing multiple objects that compete for access to awareness. In order to select relevant objects, our visual system has developed effective mechanisms that structure and organize this rather complex input. One relevant mechanism is the integration of visual object information by means of perceptual grouping. Grouping processes organize non-contiguous parts into coherent entities by segmenting regions or by linking edge segments to form continuous object boundaries (e.g., Driver, Davis, Russell, Turatto, & Freeman, 2001; Koffka, 1935; Wertheimer, 1923). A prominent example illustrating grouping processes is the illusory 'Kanizsa figure', that is, the holistic percept of a bounded and foregrounded geometric figure (triangle, square) that is actually comprised of spatially disjointed elements (Kanizsa, 1976).

Models of visual perception and attention converge on the view of object integration being the outcome of separable processes of grouping and, respectively, selective attention. However, the extent to which attention is required for integrating fragmentary object information into coherent wholes is a point of contention between the various theoretical frameworks. Some theories assume that only basic visual features are coded automatically and in parallel across the visual field at pre-attentive stages of processing, and attention is required for grouping processes to engage in the integration of features and object fragments into complete-object representations (e.g., Treisman & Gelade, 1980). Other models, by contrast, postulate that visual grouping processes operate already at low-level, pre-attentive stages prior to the engagement of selective attention (Driver & Baylis, 1998; Gilchrist, Humphreys, & Riddoch, 1996; Scholl, 2001).

The visual search paradigm (Duncan & Humphreys, 1989; Treisman & Gelade, 1980; Wolfe, 1994) provides one approach for examining whether visual object integration operates pre-attentively or requires selective attention. Relevant studies have, for instance, used search

displays containing an illusory Kanizsa figure as target presented among varying numbers of nontargets that are composed of the same "pacman" inducer elements which, however, are arranged such as not to give rise to the impression of a coherent shape – the task being to discern the presence of a Kanizsa figure as quickly and accurately as possible. The slope of the function relating detection latency, that is, reaction time (RT), to the number of configurations in the display (the display size) yields an estimate of search efficiency. If the slope is flat, search is considered efficient and operating spatially in parallel, pre-attentively. By contrast, an increase in RTs with increasing display size is taken as evidence for the involvement of selective attentive processes in discerning target presence (e.g., Treisman & Souther, 1985; Treisman & Gelade, 1980). Results of studies that employed visual search for Kanizsa figures are equivocal. A number of studies (Conci, Müller, & Elliott, 2007, 2009; Davis & Driver, 1994, 1998; Gurnsey, Humphrey, & Kapitan, 1992) reported flat slopes, indicative of Kanizsa figures being formed automatically by low-level, pre-attentive grouping mechanisms. In contrast, search for an ungrouped target configuration has turned out to be rather inefficient, indicating that an ungrouped target configuration is much harder to detect than a comparable, grouped (Kanizsa) target amongst identical nontargets (Conci et al., 2007; Conci, Töllner, Leszczynski, & Müller, 2011; Nie, Maurer, Müller, & Conci, 2016; Wiegand et al., 2015). Consistent with this, Conci et al. (2007) also observed that nontargets interfered with Kanizsa target detection when they rendered Kanizsa-like surface information, that is, partial shape groupings that increased the similarity of the nontargets to the target. In contrast, other studies (Grabowecky & Treisman, 1989; Gurnsey, Poirier, & Gascon, 1996; Li, Cave, & Wolfe, 2008) reported that RTs in search for Kanizsa figures increased with increasing display size, implying that selective attention is required for integrating the (correctly aligned) pacman elements into a coherent figure. – Thus, taken together, the question of whether or not focal attention is required to effectively bind parts into coherent

wholes has not yet been resolved conclusively.

An alternative approach used to examine whether attention is necessary for integrating separable elements into wholes is to investigate visual grouping in patients suffering from unilateral deficits in selective attention. Patients with left-sided hemi-neglect or extinction often fail to attend and respond to sensory stimuli located in the contralesional hemispace, without necessarily suffering from any primary disorder of sensation or movement (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta & Shulman, 2011; Heilman, Bowers, Valenstein, & Watson, 1987; Heilman, Watson, Valenstein, & Heilman, 1993). These deficits typically result from right-hemisphere lesions, mostly in the inferior parietal lobe. Interestingly, in extinction, a stimulus presented in the contralesional hemifield can be detected or identified when presented alone. However, when presented simultaneously with ipsilesional stimuli, the same stimulus is disregarded, or only poorly identified (Bender, 1952). That is, patients show hemi-inattention towards the contralesional, left hemifield (Karnath, 1988; Riddoch & Humphreys, 1983), often failing to respond to stimuli on the left. However, consistent with accounts of extinction in terms of a pathological, competitive bias against the contralesional hemifield (Kinsbourne, 1993; Desimone & Duncan, 1995), the lack of attention to stimuli on the left is not absolute; rather, it is relative: fewer attentional resources are allocated to the contralesional than to the ipsilesional hemifield (see also Bays, Singh-Curry, Gorgoraptis, Driver, & Husain, 2010). Most studies suggest that, despite their hemi-inattention, neglect patients nevertheless have preserved access to integrated object information across the whole visual field (e.g., Driver, Baylis, & Rafal, 1992; Gilchrist et al., 1996; Ward, Goodrich, & Driver, 1994). For instance, a single-case study by Mattingley, Davis, and Driver (1997; see also Conci et al., 2009) observed preserved access to fragmentary bilateral stimulus segments when these could be grouped across hemifields to form a Kanizsa square. Mattingley et al. presented a sequence of displays, each starting with

the presentation of four circles, arranged around fixation. On each trial, quarter-segments were briefly removed from the circles either from the left, from the right, from both sides, or not at all. The task of the patient with left-sided extinction was to detect the sides of the offsets. When the configuration of stimulus segments prevented grouping, bilateral removal of quarter-segments induced clear signs of extinction: the patient missed left-sided offsets far more often in trials with offsets on both sides compared to trials with unilateral left offsets. However, when the stimulus configuration could be grouped to form a Kanizsa square, resulting in a coherent object forming a single perceptual unit, extinction was less severe and the patient detected the offsets on both sides. This result is indicative of early, pre-attentive integration of the elements into a (illusory) figure, which can be accessed despite extinction, that is, in the absence of selective visual attention (Ro & Rafal, 1996; Vuilleumier & Landis, 1998; Vuilleumier, Valenza, & Landis, 2001).

In the above-mentioned patient studies, the typical stimulus displays merely consisted of a single grouped stimulus that had to be identified. Arguably, a more realistic, or ecologically valid, scenario may be provided by visual search paradigms, in which observers are presented with multiple stimuli. Despite this, to date, there are only few studies that examined search behaviour in patients with neglect or extinction (e.g., Aglioti, Smania, Barbieri, & Corbetta, 1997; Behrmann, Watt, Black, & Barton, 1997; Pavlovskaya, Ring, Groswasser, & Hochstein, 2002; Riddoch & Humphreys, 1987). To our knowledge, none of them explicitly evaluated object integration processes in displays that contain multiple stimuli. It is thus unknown whether the pathological bias in selective attention also gives rise to a bias in visual grouping processes during search for an illusory figure. Given this, in the present study, we combined these two approaches and investigated object integration in visual search for Kanizsa squares in patients with extinction. In more detail, we compared the effect of 'grouped' nontarget configurations, which induce partial illusory shape groupings,

versus that of symmetric but 'ungrouped' nontargets on the performance of visual search for Kanizsa squares (see Figure 1 for examples of possible stimulus configurations). Critical questions were whether, in patients with extinction, (i) the additional surface information provided by grouped nontargets would interfere with Kanizsa target detection in the same way as it does in healthy participants (Conci, Gramann, Müller, & Elliott, 2006; Conci et al., 2007) and (ii) whether the effects would be distinct for left- versus right-grouped nontargets.

If object integration processes indeed operate pre-attentively and are, thus, preserved in patients with extinction (Conci, Böbel, et al., 2009; Mattingley et al., 1997), then the interference induced by grouped nontargets should be comparable to that in healthy participants and should generally exceed that induced by baseline, ungrouped nontargets. If, however, selective attention is needed for the integration of parts into wholes (e.g., Treisman & Gelade, 1980), a diverging pattern is to be expected in patients with extinction: left-grouped nontargets containing a partial shape in the left, less attended, hemifield should interfere less than right-grouped nontargets, containing a partial shape in the right, more attended, hemifield.

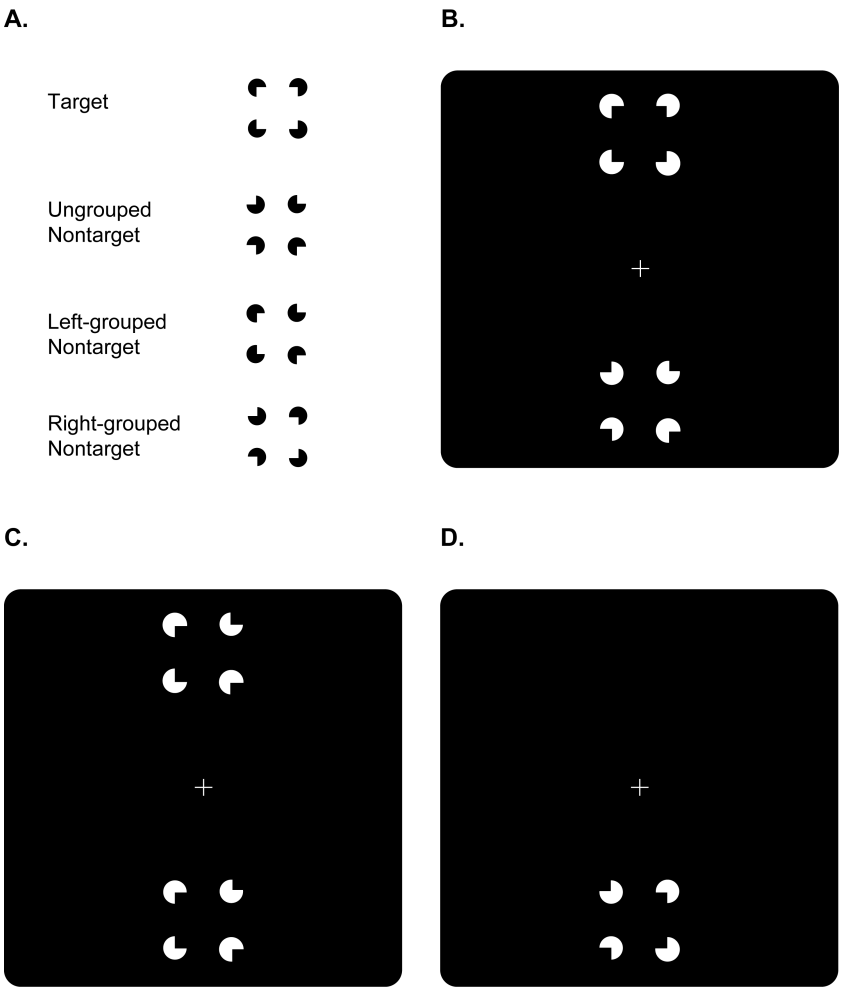

Figure 1. (A) Examples of the target Kanizsa square and of the grouped and ungrouped nontarget stimuli. Example displays: (B) two-item target-present search display, (C) two-item target-absent display, and (D) one-item target-absent display presenting an ungrouped nontarget (B), two left-grouped nontargets (C), and one right-grouped nontarget (D), respectively.

2.3.3 Methods

Participants

Five right-handed patients (4 male, 1 female; mean age: 63 years; age range: 52–72 years) who had suffered a right-hemispheric stroke and exhibited clinical signs of left-sided visual hemi-neglect were recruited from the Schoen Clinic Bad Aibling, Germany, and tested within 2–9 weeks post injury. All patients had normal or corrected-to-normal visual acuity and were

tested for visual field deficits using Goldmann kinetic perimetry. Motor functioning was preserved in all patients. All patients were tested with standardized neuropsychological neglect tests such as the conventional part of the Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), including the cancellation, visual search, line bisection, figure copying, and representational drawing subtests, or the Bells test (Gauthier, Dehaut, & Joanette, 1989). Based on these assessments, mild to moderate signs of visuo-spatial neglect were verified in each patient. Lesions were confined to either right-sided inferior-parietal and temporo-parietal or fronto-parietal areas (see Figure 2).

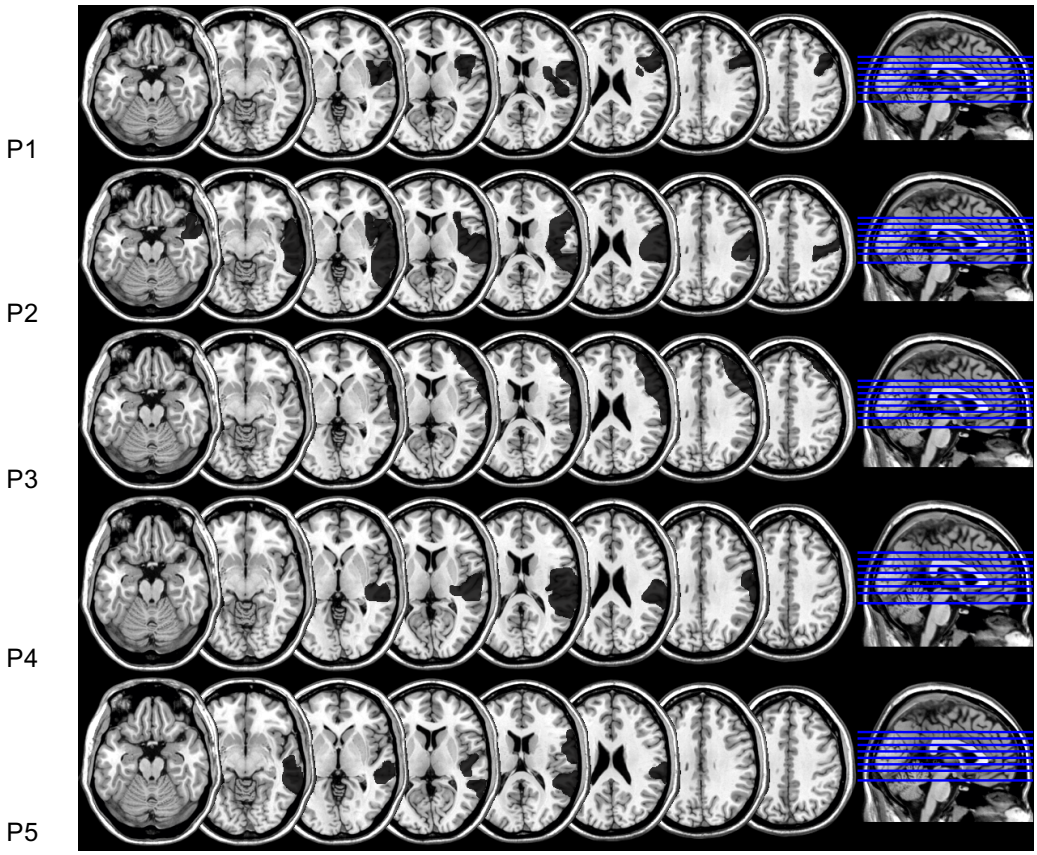

Figure 2 Lesion locations in each patient reconstructed for eight transversal slices (left) and their positions in sagittal orientation (right).

The patients were compared against an age- and gender-matched healthy control group of 10 right-handed participants (6 male and 4 female; mean age: 68.3 years; age range: 63–72

years) who were paid for their participation. Controls did not differ significantly from patients with respect to age ($t(13) = 1.71$, $p = .11$) or gender ($\chi^2(1) = 0.60$, $p = .44$). They all had normal or corrected-to-normal vision. None of them reported any history of neurological or psychiatric disease. Informed consent according to the Declaration of Helsinki II was obtained from all participants. Table 1 summarizes the demographic and clinical data of all patients and controls.

Table 1 Clinical and demographic data of patients and control participants.

	Sex	**Hand**	**Age**	**Infarction Type**	**VF Deficit**	**TSI (weeks)**
Patients						
P1	m	r	52	MCA	Q, l, s	2
P2	m	r	72	MCA	-	9
P3	f	r	57	MCA	-	5
P4	m	r	71	SC	-	8
P5	m	r	63	MCA	RH, l	7
Group Average						
Patients	4m/1f	5r	63.0			6.2
Controls	6m/4f	10r	68.3			

[Abbreviations: VF – visual field; TSI – time since injury; m – male; f – female; r – right; l – left; MCA – medial cerebral artery; SC – striato capsular; Q – quadrantanopia; RH – residual hemianopia; s – superior]

Apparatus and stimuli

The experiments were performed on an IBM-PC compatible computer using Matlab routines and Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). A standard computer mouse (which was rotated by 90°) served as response device. The distance between the

monitor and the eyes of the participants was approximately 57 cm; a head and chin rest was used to maintain head position. Stimuli were presented in light grey (3.81 cd/m^2) against a black (0.02 cd/m^2) background at 2 possible locations on a 17-inch monitor screen (1024 × 768 pixel screen resolution, 70-Hz refresh rate). Stimuli were presented centrally either above or below the fixation cross (see Figure 1 for example displays). Each stimulus configuration, composed of four pacman inducers with a diameter of 0.7°, was diagonally offset by 4.1° of visual angle from a centrally presented fixation cross. At a viewing distance of 57 cm, each candidate grouping subtended a visual angle of 2.3° × 2.3°. As depicted in Figure 1A, the target was defined as a Kanizsa square. Nontarget configurations were constructed by rotating inducer elements: for the baseline, ungrouped nontarget configuration, all four pacman inducers were rotated by 180° relative to the inducers of the target. For right-grouped nontargets, the inducers in the left half of a nontarget configuration were rotated by 180°, whereas the (other) inducers in the right half were identical in orientation to those of the target. For left-grouped nontargets, the inducers in the right half of a nontarget configuration were rotated by 180°, whereas the inducers in the left half were identical in orientation to those of the target. Accordingly, grouped nontargets were made up of partial Kanizsa shape stimuli, with partial shapes on either the left or the right side, engendering the emergence of incomplete surface information. That is, grouped nontargets gave rise to unilateral partial groupings, with the grouping location (left vs. right) being varied.

Procedure

The experiment was performed in a dimly lit experimental laboratory room. Each trial started with the presentation of a central fixation cross for 500 ms. The fixation cross was followed by the search display, to which participants had to respond. The display contained either one or two candidate objects, which were presented at central positions above and/or below the

fixation cross. In the one-item condition, either the target or one possible nontarget (ungrouped, left-grouped, or right-grouped) was presented at one of the two possible stimulus locations. In the two-item target-present condition, the target was always presented together with a nontarget (ungrouped, left-grouped, or right-grouped). In the two-item target-absent condition, two nontargets of the same type were displayed, that is, both nontargets were ungrouped, left-grouped, or right-grouped configurations (see Figure 1). Following stimulus onset, participants had to maintain central fixation and to make a speeded target-absent versus target-present response by pressing the corresponding keys of the computer mouse. Target-present/-absent responses were assigned to either the upper/lower or the lower/upper keys of the rotated mouse, in counterbalanced order across participants. Participants were instructed to respond, as quickly and accurately as possible, using the right-hand index and middle fingers; their right arm positioned such that the fingers were comfortably placed on the rotated mouse. Displays remained on the screen until participants responded, with a time-out of 2500 ms. In case of an incorrect response or a time-out, a feedback signal (a "minus" sign) was presented for 1000 ms in the centre of the screen. The inter-trial interval was 1000 ms.

Participants first performed one practice block, consisting of 20 randomly generated trials, prior to the actual experiment, to familiarize them with the task. Subsequently, 480 experimental trials were presented in 12 blocks consisting of 40 trials each. The independent variables of the experiment were the between-subjects factor group (patients, controls) and the within-subject factors target (present, absent), nontarget type (ungrouped, right-grouped, left-grouped), and display size (one item, two items). The type of nontarget was kept constant throughout a block of trials, in order to maximize the difference in search RTs between ungrouped and grouped nontargets (Töllner, Conci, & Müller, 2015) while keeping the difficulty of the task appropriate for the patients. All blocks were presented in pseudo-

random order on an observer-by-observer basis. Search displays contained a target in 50% of all trials, with targets presented equally likely above or below the central fixation cross. The dependent measures obtained and analysed were the search RTs plus estimates of perceptual sensitivity, d', and the response criterion, c, based on signal detection theory (Green & Swets, 1966). The sensitivity d' reflects the relationship of the rate of hits (i.e., correct detection of a target when one is present) to that of false alarms (i.e., erroneous 'target-present' response when no target is present) for each condition, where d' is estimated as:
d' = z(proportion hits) – z(proportion false alarms). Technically, d' represents the distance between the means of the sensory evidence distributions produced by 'noise alone' and 'signal plus noise'; accordingly, higher scores of d' indicate enhanced ability to discriminate between signal and noise. The response criterion represents the critical strength of sensory evidence required to decide 'signal plus noise' versus 'noise alone', where c is estimated as follows: c = –0,5 *(z(proportion hits) + z(proportion false alarms)). Values of c < 0 are indicative of 'liberal' responding (i.e., maximizing hits at the expense of false alarms), values > 0 of 'conservative' responding (i.e., minimizing false alarms at the expense of hits). For calculating these parameters, we corrected extreme hit rates of 1.0 and, respectively, false-alarm rates of 0 as follows: 1 − 1/(2n) for hits, and 1/(2n) for false alarms, where n refers to the number of total hits or false alarms (Macmillan & Creelman, 1991).

2.3.4 Results

Data were analysed in two sequential steps. The first analysis aimed at providing an overview of the general task performance, comparing search performance for ungrouped nontargets (i.e., baseline performance) with performance for partially grouped, that is, potentially interfering nontargets. As previous work in healthy observers had shown that partial shape information in nontargets can substantially reduce search efficiency (Conci et al., 2006;

2007), the current analysis was designed to establish, in the first instance, whether comparable effects would also be seen in patients with extinction. The subsequent analysis was performed to examine more specifically how the lateralization of attention in extinction would affect search. To this end, partial groupings in the left or right half of the nontarget items were systematically compared in terms of their relative costs on performance.

Target-nontarget interference effects

The first analysis compared search RTs as well as signal detection (d' and c) scores for partially grouped vs. ungrouped (i.e., baseline) nontarget conditions. Note that, for this initial analysis, data were collapsed across left- and right-grouped nontargets. Individual mean RTs were computed for each variable combination excluding error responses. Figure 3 presents the mean RTs for the patient group (A) and the control group (B). Each graph plots RTs as a function of display size, separately for target-absent/-present and ungrouped/grouped nontarget configuration conditions. Note that Figure 3 depicts different data points for the single-item target-present conditions. This is due to (single-item) target-present trials being sorted according to the respective nontarget types within a given block of trials. That is, even though the single target displays were physically identical in these blocks (always consisting of one Kanizsa square target), RTs to these displays differed according to the types of nontargets that were presented in the respective blocks.

RT analysis. Mean RTs were compared by means of a mixed-design analysis of variance (ANOVA), with the between-subjects factor group and the within-subject factors display size, target, and nontarget type. This ANOVA revealed significant main effects of display size ($F(1, 13) = 44.55$, $p < .01$), target ($F(1, 13) = 12.58$, $p < .01$), nontarget type ($F(1, 13) = 28.97$, $p < .01$), and group ($F(1, 13) = 15.14$, $p < .01$). Mean RTs increased with the number of to-be searched items (103 ms vs. 126 ms) and were overall faster in target-

present than in target-absent conditions (105 ms vs. 124 ms). In addition, responses were slower in the grouped compared to the ungrouped nontarget condition (121 ms vs. 108 ms), and for the patient group compared to control participants (135 ms vs. 94 ms). Moreover, several interactions were significant. First, the target × group interaction ($F(1, 13) = 10.67$, $p < .01$) was due to the patients exhibiting slower responses (by 37 ms) to target-absent than to target-present displays, while the control participants showed no difference (2 ms). Furthermore, the display size × target × group interaction was significant ($F(1, 13) = 6.33$, $p = .03$), due to patients showing consistent increases, with display size, in target-present and target-absent RTs (increases of 22 and 29 ms/item, respectively, $p = .24$), while for controls target-present slopes were somewhat steeper than target-absent slopes (22 and 19 ms/item, respectively, $p = .07$). Finally, a significant display size × target × nontarget type interaction ($F(1, 13) = 6.85$, $p = .02$) showed that additional surface information in grouped nontargets reduced search efficiency particularly on target-absent trials (search slopes in ungrouped and grouped nontargets were 17 and 26 ms/item, respectively, $p = .01$), while no difference in search efficiency was evident for target-present trials (ungrouped and grouped nontarget slopes: 22 and 23 ms/item, respectively, $p > .05$). No other significant effects were obtained (all ps $> .11$). In summary, patients were slowed overall, but particularly so when the target was absent and when the display size was high. Importantly, however, there was no indication that the overall effect induced by grouped nontargets differed between groups. That is, nontargets that induce partial shape groupings seemed to affect RTs similarly in both groups, particularly on target-absent trials. This suggests that patients based their search on an integrated (grouped) target representation, rather than on the constituent, individual local elements; in the latter case, search would have been expected to be much more inefficient (Conci et al., 2007).

Sensitivity and criterion analysis. Accuracy data was used to obtain estimates of perceptual sensitivity and response criteria in target-present/-absent decisions. The overall level of accuracy was reasonably comparable in patients and controls ($t(13) = -1.67$, $p = .12$), with a mean error rate of 5.3% ($SD = 6.91$) and 1.8% ($SD = 1.23$), respectively. Next, d' and c scores were analysed using (separate) mixed-design ANOVAs, with the between-subjects factor group and the within-subject factors display size and nontarget type, analogous to the RT analysis above (note that RT and sensitivity/criterion measures are essentially unrelated and may therefore reveal a diverging pattern of effects). Both ANOVAs revealed the main effect of display size to be significant: sensitivity scores d' were reduced for two-item compared to one-item displays (mean d': 3.8 vs. 4.2, $F(1, 13) = 14.57$, $p < .01$); at the same time, the response criterion was set somewhat more conservatively for two-item compared to one-item displays (mean c: .28 vs. .01, $F(1, 13) = 17.42$, $p < .01$). No other significant effects were obtained (all ps > .09).

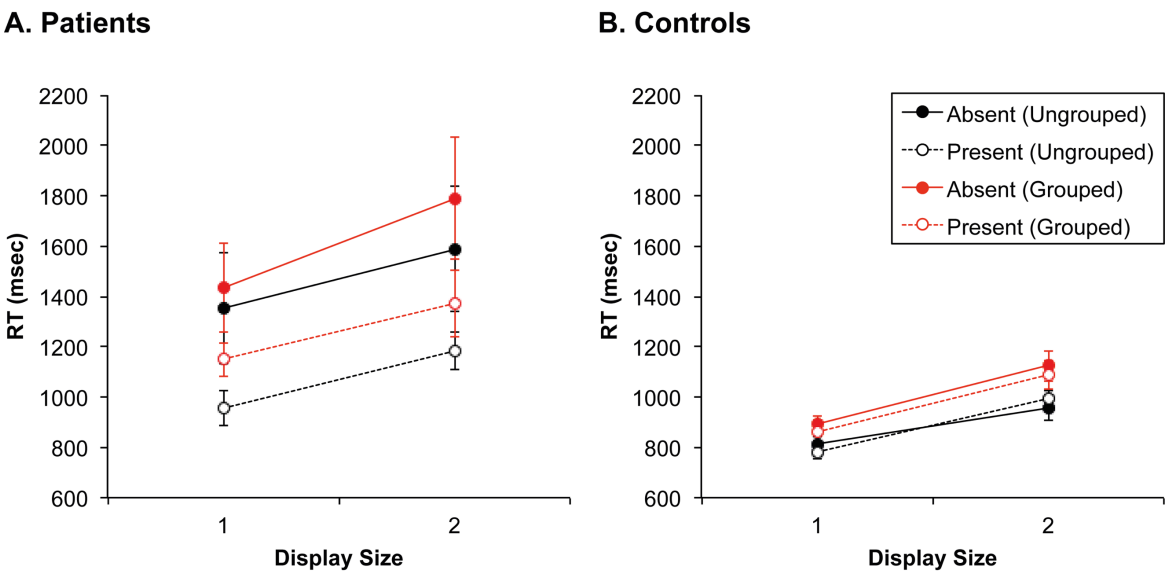

Figure 3 Mean RTs in the patient (A) and the control (B) group as a function of display size (1 item, 2 items) for the different target (solid line: absent, dotted line: present) and nontarget type (black: ungrouped, red: grouped) conditions. Error bars represent ±1 standard error of

the mean. Note that, as the nontarget type was kept constant throughout a block of trials, the data points obtained differed between the nontarget type conditions; this also applies to the single-item condition, in which the respective nontarget was presented only on target-absent trials (but not on target-present trials).

Nontarget lateralization

A second set of analyses was performed to examine whether and how target-nontarget interference differs when partial shape information in nontargets is present in the less attended versus the more attended hemifield. To this end, we determined the costs engendered by the distinct, unilateral groupings, by subtracting RTs and, respectively, d' and c in the ungrouped nontarget condition from those in the left- and right-grouped nontarget-type conditions. Figure 4 depicts the RT costs (in ms) as a function of the nontarget grouping location for both patients and controls. Separate graphs depict the results for one-item displays (target-absent) and two-item displays (for target-present and target-absent conditions, respectively). Note that, because of the (logical) lack of nontargets in target-present one-item displays, costs could not be computed for this condition.

RT analysis.

One-item displays. For the RT analysis, one-item displays were analysed by a mixed-design ANOVA with the between-subjects factor group (patients, control) and the within-subject factor nontarget grouping location (left-grouped, right-grouped nontarget), which did not reveal any significant effects (all *p*s > .10). As depicted in Figure 4A, the RT costs were statistically comparable for left- and right-grouped nontargets (99 ms vs. 59 ms; non-significant main effect of grouping location). Also, the costs were comparable between patients and controls (81 ms vs. 77 ms; non-significant main effect of group). These findings show overall comparable RT patterns in both patients and controls, and no evidence for any

type of strategy, such as a tendency of the patients to perform the task by primarily responding to the cut-out segments in the right, unimpaired hemifield.

Two-item displays. A mixed-design ANOVA on two-item displays with the between-subjects factor group (patients, control) and the within-subject factors nontarget grouping location and target (absent, present) yielded no significant main effects (all *p*s > .16). However, the nontarget grouping location × group interaction ($F(1, 13) = 8.26$, $p = .01$) was significant: while costs were statistically comparable for left-grouped nontargets in both patients and controls (103 ms vs. 180 ms) ($t(13) = .975$, $p = .35$), the costs for right-grouped nontargets were much greater in patients than in control participants (285 ms vs. 83 ms) ($t(13) = –2.48$, $p = .03$). No other significant effects were obtained (all *p*s > .34). To summarize, in patients with extinction, the RT costs induced by grouped nontargets in visual search for a Kanizsa figure were comparable to those of control participants only with single-item displays. When display size increased to two items, patients showed systematic unilateral deficits, namely: enhanced costs for nontarget objects with a partial shape in the right, that is, the more attended hemifield.

Sensitivity and criterion analysis. For one-item displays, analogous ANOVAs of the d' and c costs did not reveal any significant main or interaction effects (all *p*s > .26, overall mean costs in d' = –.06 and in c = .07). For two-item displays, the ANOVAs revealed a significant main effect of nontarget grouping location ($F(1, 13) = 13.01$, $p < .01$) for d': sensitivity costs were increased with left- as compared to right-grouped nontargets (–.47 vs. .07). Note that more negative values of d' costs, as depicted here, are indicative of a reduction in sensitivity for the grouped relative to the ungrouped condition. No other significant effects were obtained (overall mean costs in c: –.52; all *p*s > .25). The lack of group effects indicates that patients and controls differ neither with respect to the response criterion (i.e., the strength of sensory evidence required to respond target-present rather than

target-absent), nor with respect to perceptual sensitivity (i.e., the ability to discriminate signal from noise), despite of an overall reduction in sensitivity in both groups for left-grouped nontargets.

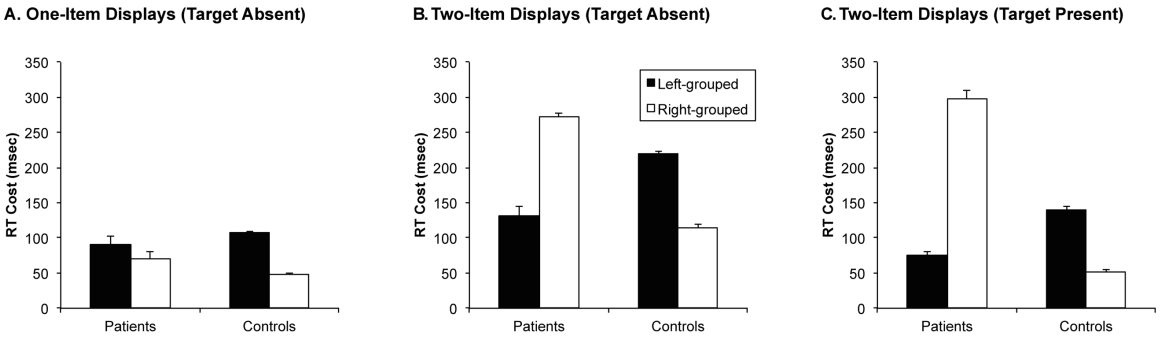

Figure 4 Mean RT costs as a function of nontarget grouping location (black: left-grouped, white: right-grouped) for patients and controls, separately for one-item displays [target-absent (A)] and two-item displays [for target-absent (B) and -present (C) conditions, respectively]. Error bars represent ±1 standard error of the mean.

2.3.5 Discussion

The present study was designed to assess the relationship between selective attention and object integration (in the left and the right visual field) in a visual search paradigm that presented to-be-grouped targets and nontargets to both extinction patients with unilateral deficits of selective attention and healthy controls. Our main results were that (i) partially grouped nontargets induced overall comparable interference in patients and controls and that (ii) for single item configurations, effects of left-sided groupings were comparable to those of right-sided groupings in both participant groups. Finally, (iii) clear effects of extinction manifested in particular with two-item displays, where stronger RT costs emerged for nontargets that were similar to the targets in the intact, more attended hemifield, compared to the less attended hemifield. From these findings, we conclude that a bias in attention leads to biased grouping operations in competitive search situations in particular, i.e., preserved

grouping in the right, attended, and compromised grouping in the left, less attended, hemifield. In our view this points to a crucial contribution of selective attention to visual object integration processes.

Target-nontarget shape interference. In an initial, overall analysis, we assessed the effect of partial shape information in nontargets on visual search for a target Kanizsa figure, without differentiating between left- and right-grouped nontargets. Results revealed a pronounced slowing of search for grouped nontargets relative to the ungrouped (i.e., baseline) condition with increasing display size and particularly on target-absent trials. This reduction in search speed brought about by grouped nontargets was in general comparable between patients and controls, suggesting an overall similar pattern of nontarget interference. However, extinction patients were particularly slowed when no target was present. Signal detection analysis further revealed a similar pattern of performance in patients and controls, with a reduced sensitivity and a slight shift in the decision criterion (towards more conservative responding) for two-item compared to one-item displays.

Our finding that partial shape information in nontargets reduces search efficiency in both patients and controls is in line with previous reports from healthy participants (Conci et al., 2006; Conci et al., 2007; Töllner et al., 2015). This pattern of interference can be explained in terms of similarity-based (interference) search models (Duncan & Humphreys, 1989), which assume that an increase in similarity between targets and nontargets reduces the efficiency of target detection. In terms of biased-competition accounts (Desimone & Duncan, 1995), grouped nontargets would gain more attentional weight, compared to ungrouped nontargets, due to their better match with the task-relevant Kanizsa square target; as a result, the grouped nontarget would be favoured for visual selection (Conci et al., 2006; Conci et al., 2007). In the context of the current experiment, with Kanizsa figures (i.e., grouped objects) presented as targets, it is reasonable to assume that target-nontarget similarity is largely

determined by integrated object attributes, that is, the output of object completion processes that involve grouping mechanisms, such as grouping by closure/good continuation. In this view, target selection and similarity-based interference effects in both healthy participants and patients are driven by integrated object information (Conci et al., 2007).

In line with the assumption that grouping and similarity interact, search efficiency was previously shown to be markedly reduced for ungrouped relative to grouped target configurations, even though the similarity between targets and nontargets was the same in both cases (Conci et al., 2007). Thus, if patients' search was based on the individual local elements (i.e., the ungrouped pacman inducers) rather than an integrated (grouped) target representation, a divergent pattern of performance would be expected, with patients exhibiting significantly reduced search efficiency compared to controls. This was clearly not the case. Hence, the pattern of search performance observed in the present study most likely reflects processing of grouped objects, rather than being akin to search for ungrouped items that do not require object integration to the same extent.

The finding that target-absent trials in particular exhibited a difference in search efficiency between grouped and ungrouped nontargets indicates that partial surface information primarily affected search when participants allocated attentional resources to the nontargets. In contrast, according to a biased-competition account of attention (Bundesen, 1990; Desimone & Duncan, 1995), on target-present trials, nontarget stimuli compete with the more salient target stimulus. Attentional weight, which is biased towards the most salient stimulus, is thus withdrawn from the nontargets. Equal search performance for target-present grouped and ungrouped nontarget trials thus indicates that when less attentional capacity was allocated towards partial groupings, these might have been reduced in priority (in both healthy controls and extinction patients). We interpret this finding as an indication that attentional resources can modulate partial shape groupings.

Spatial attentional bias modulates grouping. Follow-on comparisons of interference effects induced by left- versus right-grouped nontargets revealed a specific pattern related to extinction, with a crucial difference between conditions with two-item, relative to one-item, search displays. With displays containing only one item, extinction patients showed the same pattern of search interference effects as healthy participants, without any differential RT costs between left- and right-grouped nontargets. This indicates that patients were able to integrate the stimulus configurations presented into completed shapes, without differences as to whether a given partial shape was present on the left, less attended, or on the right, more attended, side. That is, in essence, both types of grouped nontargets could be differentiated reliably from the completed square in the target Kanizsa figure. This finding in principle confirms previous reports in patients with unilateral deficits in selective attention, who, in general, showed preserved grouping with displays that presented a single, to-be-grouped object configuration (e.g., Conci, Böbel, et al., 2009; Driver et al., 1992; Mattingley et al., 1997; Ro & Rafal, 1996; Vuilleumier & Landis, 1998; Vuilleumier et al., 2001). Thus, in one-item displays, access to left- as well as right-grouped stimulus configurations was unaffected by extinction, that is: object integration mechanisms were functioning uncompromised across both halves of the visual field. This agrees with behavioural and electrophysiological studies of healthy participants, which revealed search for Kanizsa figures to be efficient, with object completion being associated with early stages of visual processing (e.g., Abu Bakar, Liu, Conci, Elliott, & Ioannides, 2008; Conci, Böbel, et al., 2009; Conci et al., 2011; Wiegand et al., 2015). Our findings also agree with studies reporting an influence of unconscious access to contralesional visual information in extinction patients (Conci, Böbel, et al., 2009; Driver & Vuilleumier, 2001; Finke et al., 2009; Marshall & Halligan, 1994; Mattingley et al., 1997). Accordingly, at least in conditions that require basic perceptual processing of a single candidate target object, patients with

deficits in attentional orienting are not necessarily impaired in integrating parts into wholes – thus, in principle supporting object-based accounts of attention (see also Driver et al., 1992; Ward et al., 1994).

In contrast to 'normal' performance with single-item presentations, when attention had to be distributed among multiple stimuli (i.e., in two-item displays), a spatially lateralized interference pattern emerged in extinction patients: relative to controls, patients showed a marked increase in interference when nontargets induced a partial shape grouping on their right, more attended, side – whereas nontargets with a partial shape grouping on the left, that is, their less attended, side interfered comparably (or numerically even less) relative to control participants. Restated, extinction patients showed less efficient search than controls when presented with multiple (i.e., two) objects that contained similar shape information as the target in the right hemifield; by contrast, interfering information in the left hemifield did not lead to elevated costs at all.

In the control group, we found a tendency towards the opposite effect: left-grouped nontargets interfered (at least numerically) more than right-grouped nontargets. Thus, in healthy participants, object integration processes were biased towards the left when attentional resources had to be distributed in a competitive search situation. This may be associated with a slight, though highly replicable, attentional bias towards the left in healthy participants with both unilateral and bilateral stimulation, which has been referred to as 'pseudo-neglect' (Jewell & McCourt, 2000) and 'pseudo-extinction' (Goodbourn & Holcombe, 2015), respectively.

The spatially lateralized pattern of interference with two-item displays might be explained in terms of biased competition among visual inputs for limited processing capacity (Bundesen, 1990; Desimone & Duncan, 1995). In a non-competitive search situation, that is, when only a single item is presented in the display, there is no need for attention to be

distributed. Accordingly, despite the well-documented attentional bias towards ipsilesional stimuli in extinction (e.g., Baylis & Driver, 1993; Humphreys, Romani, Olson, Riddoch, & Duncan, 1994), a left- or right-grouped nontarget would receive the full amount of available capacity, enabling a decision to be made between target presence and absence. However, distributing attention among multiple candidate target stimuli (in two-item displays) reduces the amount of attention that can be allocated to each single stimulus. In this situation, extinction patients allocate attentional weight predominantly to the right hemifield (Duncan et al., 1999), as a result of which target-nontarget similarity is primarily evaluated in the right (rather than the left) half of a given stimulus configuration. Due to this extinction-specific spatial attentional bias, right-grouped nontargets have a competitive advantage in the race for selection.

Overall, this pattern of results suggests a crucial link between perceptual grouping and attention: faced with multiple stimuli, extinction patients are impaired in engaging mechanisms of perceptual grouping in the contralesional field that would permit the target to be discerned from more or less similar nontargets. Thus, contrary to the interpretations drawn from a number of previous studies of extinction patients (e.g., Conci, Böbel, et al., 2009; Driver et al., 1992; Gilchrist et al., 1996; Mattingley et al., 1997; Ward et al., 1994), grouping operations are not (completely) automatic and (fully) available at pre-attentive stages; rather, attention is required to effectively bind parts into coherent wholes. It follows, in line with the notion of a competitive bias against left-sided information in extinction (Driver, Mattingley, Rorden, & Davis, 1997; Duncan, Humphreys, & Ward, 1997; Kinsbourne, 1993), that object integration depends on the degree of competition among the elements in the visual input: integration is successful only if sufficient attentional capacity is available, in which case the spatial bias in extinction patients is considerably reduced. By contrast, when there is competition among several stimuli, the (distributed) attentional resources are insufficient to

permit object integration, leading to a strong bias. This implies that the pathological attentional bias gives rise to a grouping bias, with less effective grouping in the unattended field.

While processes of object integration were clearly impaired in extinction patients presented with multiple objects, the account sketched above – in terms of multi-item 'competition' and 'distributed attention' – would imply that some basic grouping processes are actually functioning relatively normally. The notions of competition and distributed attention presuppose that there are primitive entities that compete for the allocation of attention or across which attentional resources can be distributed. In this view, a first, unselective wave of processing would determine potentially relevant clusters, whereas the selection of grouped items is then determined in a second wave of processing, which crucially depends on attention (Bundesen, Habekost, & Kyllingsbaek, 2005). Phenomenally, the pacman stimuli in Figure 1B and 1C form two clusters discernible (even or especially) at low spatial scale: one above and one below the fixation cross. That these stimuli are clustered into separate entities already implies a grouping process: grouping based on proximity (and perhaps similarity), and this process would have to operate logically prior to the allocation or distribution of attention (e.g., attention can only be spread across both clusters if these are in some way represented, for instance, on some attention-guiding saliency map). This base-level process would precede Kanizsa-type Gestalt formation, where the processes involved in the latter – contour interpolation and region filling-in – may be dependent on attention. In other words, there are likely to be more primitive grouping processes that presumably operate pre-attentively (rough formation of clusters) and more complex processes that render the boundary contour and enclosed, filled-in regions (object integration), which are dependent on attention (see also Roelfsema, 2006 for a comparable theoretical framework). Although the task used in the present study was not designed to dissociate these two stages of grouping, the

pattern of deficits displayed by the extinction patients (increased difficulty with multiple objects) implies that it is the latter, more sophisticated processes of object integration that are especially compromised by the non-availability of attentional resources.

Taken together, our results in patients and healthy participants indicate that object binding requires attention, thus challenging accounts according to which pre-attentive processing suffices to render and represent complete objects (Driver & Baylis, 1998; Scholl, 2001, for reviews). Our results imply that integrating features into complete objects can only be achieved efficiently when sufficient attention is distributed across fragmentary, to-be-grouped visual elements.

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3 General conclusions and future directions

Studies I and II of the first part of this dissertation combined parametric assessment of attentional functions based on TVA (Bundesen, 1990) with a tDCS intervention to (i) specify attentional dysfunctions in MDD and, respectively, schizophrenia in terms of establishing a concrete parameter profile, and (ii) to examine for potential tDCS-induced effects on attentional processing.

Taken together, with regard to question (i) above, the TVA-based assessment proved to be a sensitive method for unveiling attentional deficits in both MDD and schizophrenia. In MDD patients, the parametric attention assessment yielded a selective impairment in visual processing speed as a core constraint in attentional processing. In schizophrenia patients, the assessment revealed an impairment of general attentional capacity as the primary factor compromising visual attentional functioning. These findings corroborate the TVA-based approach's usefulness not only for neuroscientific but also clinical questions. Specifically, the clinical utility of the approach lies in its potential to complement basic diagnosis in terms of a detailed parameter profile of attentional deficits (for review Habekost, 2015). Determining a detailed attentional profile is important in many respects. It provides useful information for therapeutic approaches, for instance, for the individual adjustment of therapeutic measures according to the specific attentional deficits. Furthermore, as neuro-cognitive functions are considered crucial determinants for the functional outcome of patients (Buist-Bouwman et al., 2008; Jaeger, Berns, Uzelac, & Davis-Conway, 2006; McIntyre et al., 2013), outcome measures can be predicted more reliably based on a better identification of the degree of cognitive impairments. Moreover, a detailed characterization of disorder-specific impairments of attentional sub-components can be used for a more refined distinction of various disorders in terms of neuro-cognitive deficits. Standard neuro-cognitive tests often fall short in providing such a detailed attentional profile in clinical conditions such as MDD

and schizophrenia, characterized by abnormalities in large-scale brain networks (for review Habekost, 2015).

The present results add to the theoretical understanding of attentional dysfunctions in MDD and schizophrenia. Future studies can build on these findings in several ways. In particular, studies combining TVA-based assessment with neuroimaging measures would be of major interest. This combination is particularly promising for expanding our understanding of the neural underpinnings of disease effects on attentional parameters in psychiatric conditions – a question that has received only limited attention to date. Likewise, studies that aim to establish the relation between TVA parameters and clinically relevant behaviour or biological disease markers would further enhance the clinical relevance of such comprehensive approaches (Habekost, 2015).

With regard to question (ii), the tDCS-induced modulation of attentional parameters, the combined TVA-tDCS approach turned out to be useful in teasing apart the rather subtle stimulation effects on different neuro-cognitive components. In MDD patients, tDCS influenced only the processing speed parameter *C*, whereas there was no indication of changes in the other TVA attention parameters. More specifically, the visual processing speed deficit was ameliorated by activating the prefrontal alertness system by means of tDCS in MDD patients. This suggests that even a single session of anodal tDCS over the dlPFC has relatively enduring effects – going beyond the stimulation intervention – on alertness-dependent visual processing speed.

The present results in MDD patients are promising and inspire further questions for future therapeutic and experimental studies in MDD. For instance, future studies should combine tDCS with functional brain imaging techniques, such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). Such a combined approach could expand our understanding of the underlying mode of action of prefrontal tDCS effects

with regard to large-scale brain networks, and help develop carefully targeted administration of tDCS for research and clinical purposes (Meinzer et al., 2014). Another question to address in future studies concerns whether, and to what extent, combining tDCS with an additional behavioural intervention, such as cognitive training, could enhance and prolong tDCS-induced effects in MDD patients (Martin, Liu, Alonzo, Green, & Loo, 2014; Martin et al., 2013). Given that cognitive training and neuromodulation, by means of tDCS, both affect neuroplasticity, their combination could promote greater, synergistic effects (Looi et al., 2016) – an open question that requires further investigation.

To be clinically relevant, tDCS should induce more stable changes in cortical function and behaviour. Such long-term tDCS effects might be achieved by repetitive stimulation protocols (Nitsche & Paulus, 2011). Therefore, as a next step, more comprehensive, repetitive treatment studies would have to determine to what degree repetitive stimulation leads to more pronounced and enhanced consolidation of the tDCS-induced benefits in MDD (Boggio, Asthana, Costa, Valasek, & Osorio, 2015). The currently proceeding multicentre study 'Transcranial direct current stimulation as treatment for major depression – a prospective multicentre double blind randomized placebo controlled trial' (Padberg et al., 2017) in which patients receive a 6-weeks treatment with tDCS – was designed to explore this question in more detail. Among others, this clinical trial includes an adjunctive TVA-based attentional assessment, carried out by our research group, to investigate the sustained efficacy of repetitive tDCS on neuro-cognitive parameters. Patients are tested with the TVA-based attentional assessment before tDCS treatment (baseline), during the treatment (at week 4 and 6) and in a follow-up session at week 30. This study will complement the present data and reveal whether tDCS-induced neuro-cognitive benefits in MDD patients can be boosted and prolonged by repetitive tDCS applications.

In contrast to the beneficial tDCS effects on visual processing speed in MDD patients revealed in study I, the findings of study II, with schizophrenia patients, were less promising. In particular, prefrontal tDCS did interfere with (rather than enhance) practice effects on visual processing speed. In light of this outcome, it cannot be ruled out that the stimulation parameters applied may entail cognitive safety risks for schizophrenia patients. This finding of a potential tDCS-induced disruption effect on the cognitive domain investigated here in schizophrenia highlights the need for more neuroscience-based research on schizophrenia and safety assessments in future tDCS studies involving psychiatric patients. For instance, prior to the setup of large-scale clinical trials, future studies would be well advised to systematically evaluate tDCS effects, in terms of dosage and electrode positioning, on cognitive parameters in schizophrenia.

The study reported in the second part of this dissertation dealt with the behavioural consequences of impairments in basal cognitive functions on information processing. Specifically, study III investigated the effects of selective attentional deficits on perceptual processes with a focus on object integration through perceptual grouping, drawing on visual search performance of neuropsychological patients suffering from extinction as a result of brain damage. The results revealed that an extinction-specific bias in attention leads to biased grouping operations in competitive search situations in particular: grouping operations were preserved in the right, attended hemifield, whereas they were compromised in the left, less attended hemifield. The pattern of results, in patients and healthy participants, indicates that object binding requires attention, thus challenging accounts according to which pre-attentive processing suffices to render and represent complete objects (for review Driver & Baylis, 1998; Scholl, 2001). Instead, integrating features into complete objects can, arguably, only be achieved efficiently when sufficient attention is distributed across fragmentary, to-be-grouped visual elements.

Study III is not only relevant from a clinical point of view, but it also provides important evidence for informing fundamental research. That is, by employing a patient-based approach, study III contributed to our understanding of the role of selective attention in visual object integration processes – a long-standing and much debated issue in the basic research field of visual attention. In brief, study III goes beyond merely clinical studies (such as studies I and II) and provides an example of how patient studies can provide a useful approach for the examination of basic research questions.

Future studies that apply this experimental approach, based on visual search, to other patient populations, for instance psychiatric patients, might prove very interesting as well. For example, future studies might investigate the extent to which attentional impairments in psychiatric conditions, such as those revealed in studies I and II of this dissertation, are reflected in everyday life tasks applying typical perceptual situations such as visual search. Visual search is a central task in everyday life, which, in healthy humans, involves attentional processes controlling the perception of salient and less salient stimuli. By implication, alterations in visual attention, as observed in different clinical conditions, may give rise to visual search deficits that, eventually, may also help explain everyday life consequences in the respective patients.

Previous research has shown that reduced visual processing speed impairs the perception and interpretation of complex visual material (e.g., Finke et al., 2007; Neitzel et al., 2016). Likewise, basal attentional dysfunctions in psychiatric conditions might lead to alterations in visual perception – specifically perceptual grouping operations – in these patients. A study of our research group is currently underway to investigate this question further in patients with schizophrenia. To this end, we employed a variant of a visual search task with Kanizsa figures, similar to that used in study III. In healthy observers, search performance has been shown to be substantially modulated by grouping of a coherent global

shape from local stimulus fragments (Conci, Müller, & Elliott, 2007). Whether this also holds true for schizophrenia patients will be revealed by examining search performance in these patients. This will shed light on how schizophrenia influences the structuring of visual information and the allocation of attention to a grouped target. More detailed information about a potential relationship between attentional dysfunctions and perceptual processes in schizophrenia might, ultimately, contribute to a better understanding of the disorder.

By the same token, future studies that apply the experimental approach taken in studies I and II, in which a TVA-based attentional assessment was combined with tDCS, to patients with extinction might also prove very interesting. In an ongoing pilot study, our research group has pursued this approach in a group of neglect and extinction patients to explore the specific attentional impairments as well as tDCS-induced effects on attentional parameters in these patients. Similarly, combining tDCS with a visual search task, such as the one employed in study III of this thesis, would be an equally interesting avenue to be taken in future studies. This could shed light on the efficacy of tDCS to augment visual search performance, for example, by reducing a decrement in vigilance.

To conclude, the three studies reported in this dissertation contribute to our understanding about pathological as well as normal visual attentional processing. The first two studies relied on a framework of normal visual attention based on Bundesen's TVA (Bundesen, 1990) to provide a comprehensive description of the pattern of attentional deficits in MDD and schizophrenia patients and their modulation by means of tDCS. The study in the second part employed a different approach based on the investigation of patients with selective deficits in attention, the aim being to help resolve a long-standing debate in the field of visual attention research, namely, the contribution of selective attention to object integration processes. Taken together, the findings of the three studies provide a promising basis for future therapeutic and experimental investigations.

Deutsche Zusammenfassung

Psychiatrische und neurologische Erkrankungen gehen häufig mit Defiziten der visuellen Aufmerksamkeit einher, die oftmals auch über die klinische Remission hinaus bestehen bleiben (Heaton et al., 2001; Schaefer, Giangrande, Weinberger, & Dickinson, 2013; Trivedi & Greer, 2014; Tyson, Laws, Flowers, Tyson, & Mortimer, 2006; Weiland-Fiedler et al., 2004). Visuelle Aufmerksamkeitsprozesse beinhalten verschiedene räumlich lateralisierte und nicht lateralisierte Subkomponenten, wie beispielsweise attentionale Selektivität, Verarbeitungsgeschwindigkeit oder Kurzzeitgedächtnisspeicherkapazität (Bundesen, 1990, 1998). Defizite in jeder einzelnen Subkomponente können prinzipiell zu einer verminderten Aufmerksamkeitsleistung führen. Die spezifischen attentionalen Subkomponenten, die den kognitiven Defiziten dieser Erkrankungen zugrunde liegen, sind jedoch nur unzureichend aufgeklärt.

Eine präzise Erfassung der attentionalen Leistungseinbußen ist von großer Wichtigkeit. Spezifisches Wissen über diese Defizite liefert wertvolle Informationen für Therapieansätze, die daraufhin entsprechend angepasst werden können. Außerdem dient eine präzise Diagnostik des Ausmaßes kognitiver Defizite einer zuverlässigen Vorhersage des Erkrankungsverlaufs. Darüber hinaus ermöglicht sie eine bessere Abgrenzung verschiedener Erkrankungen in Hinsicht auf charakteristische neuro-kognitive Defizite.

Hierfür werden Methoden benötigt, die eine zuverlässige Bestimmung der Defizite im klinischen Kontext erlauben. Insbesondere muss ein Instrument zur Messung von Aufmerksamkeit die verschiedenen attentionalen Einzelfunktionen erfassen können. Ein Verfahren, das sich hierfür sehr gut eignet und daher die theoretische und experimentelle Grundlage des ersten Teils dieser Dissertation bildet, ist die parameterbasierte Messung von Aufmerksamkeitsfunktionen, basierend auf Bundesens mathematisch begründeter Theory of Visual Attention (TVA) (Bundesen, 1990). Dieses Verfahren weist, im Gegensatz zu

konventionellen neuropsychologischen Tests, eine große Testsensitivität auf und ermöglicht die Schätzung von vier mathematisch unabhängigen Aufmerksamkeitsparametern. Diese sind die allgemeine Verarbeitungsgeschwindigkeit *C*, die Speicherkapazität des visuellen Kurzzeitgedächtnisses *K*, die Top-Down-Kontrolle α und die räumliche Aufmerksamkeitsverteilung w_λ.

Der erste Teil der vorliegenden kumulativen Dissertation beinhaltet zwei doppelt-verblindete, placebokontrollierte und randomisierte Studien, in denen dieses parameterbasierte Verfahren eingesetzt wurde. Ziel war es hierbei, die visuellen Aufmerksamkeitsleistungen bei klinisch depressiven (Studie I) und schizophrenen Patienten (Studie II) in Hinblick auf mögliche Einbußen gegenüber gesunden Kontrollprobanden zu untersuchen. Als ursächlich für die Aufmerksamkeitsdefizite werden Aktivitätsveränderungen in dorsolateralen präfrontalen Alertness-Netzwerken diskutiert (z.B. Barch & Ceaser, 2012; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Eine Wiederherstellung dieser Aktivitätsveränderungen mittels transkranieller Gleichstromstimulation (tDCS) könnte also Alertness-abhängige kognitive Defizite in diesen Patienten verbessern. Daher war ein weiteres Ziel dieser Studien, die Auswirkung einer einmaligen anodalen Gleichstromstimulation (2 mA, 20 Minuten) über dem dorsolateralen präfrontalen Kortex auf bestimmte Aufmerksamkeitsfunktionen zu untersuchen. Zu diesem Zweck wurden die TVA-basierten Aufmerksamkeitsparameter vor, unmittelbar nach und 24 Stunden nach der Stimulationsbehandlung gemessen. Bei Patienten mit majorer Depression ergab die parametrische Aufmerksamkeitsmessung eine signifikante Reduktion der Verarbeitungsgeschwindigkeit (*C)* gegenüber den gesunden Kontrollprobanden. Die Aufmerksamkeitsschwierigkeiten der Patienten mit majorer Depression sind also auf eine verlangsamte Aufnahme visueller Informationen zurückzuführen. Es ist auszuschließen, dass diese Verlangsamung motorischer Natur ist, da die TVA-basierte Aufmerksamkeitstestung

lediglich die reine Aufmerksamkeitsleistung, bereinigt um die motorische Komponente, erfasst. Das Defizit in der Verarbeitungsgeschwindigkeit konnte mittels einer einmaligen Gleichstromstimulationsbehandlung des präfrontalen Alertness-Systems verbessert werden. Dieser Effekt wurde 24 Stunden nach Beendigung der Stimulation beobachtet. Aus neurophysiologischer Sicht ist dieser Stimulationseffekt auf die Verarbeitungsgeschwindigkeit möglicherweise auf tDCS-induzierte N-Methyl-D-Aspartat (NMDA) Rezeptor-abhängige Plastizitätseffekte zurückzuführen. Auf Netzwerkebene könnten diese Nacheffekte tDCS-induzierte Veränderungen der funktionellen Konnektivität in frontoparietalen Alertness-Netzwerken indizieren, die sich auf Verhaltensebene in retardierten Effekten manifestieren. Diese Ergebnisse deuten an, dass sogar eine einmalige präfrontale Gleichstromstimulationsbehandlung länger anhaltende neuro-kognitive Effekte bewirken kann. Dies spricht für eine über Zeitperioden unspezifischer tDCS-induzierter Erregbarkeitssteigerung hinausgehende Erhöhung der kortikalen Untererregung.

Schizophrenie-Patienten zeigten gegenüber gesunden Kontrollprobanden eine signifikante Reduktion der allgemeinen Verarbeitungskapazität (*C* und *K*), die den Aufmerksamkeitsschwierigkeiten zugrunde zu liegen scheinen. Bezüglich einer kognitionsverbessernden Wirksamkeit der tDCS ergaben die vorliegenden Ergebnisse vielmehr einen interferierenden als verbessernden Effekt auf einen übungsabhängigen Anstieg der Verarbeitungsgeschwindigkeit der anodalen präfrontalen tDCS. Anhand dieser Ergebnisse kann nicht ausgeschlossen werden, dass die angewandten Stimulationsparameter ein kognitives Sicherheitsrisiko für Schizophrenie-Patienten darstellen. Bei gesunden Kontrollprobanden zeigten sich keine tDCS-induzierten Effekte.

Die Untersuchung von Patienten mit Aufmerksamkeitsstörungen ermöglicht allgemeinpsychologische Fragestellungen anzugehen, die sich mit der Rolle von Aufmerksamkeitsfunktionen für die Informationsverarbeitung befassen. Außerhalb der

klinischen Forschung besteht demgemäß die Möglichkeit, Patienten als Modell dafür zu nutzen, um bei einem Ausfall bestimmter Funktionen Rückschlüsse über ihre Bedeutung zu gewinnen. Speziell die Untersuchung von Patienten mit Extinktion, die eine rechtshemisphärische Hirnschädigung erlitten haben, ist in diesem Zusammenhang von großem Interesse.

Eine relevante allgemeinpsychologische Frage betrifft die Bedeutung selektiver Aufmerksamkeit für Wahrnehmungsprozesse. Wahrnehmung und Aufmerksamkeit sind im Dienste der Handlungssteuerung zwei eng miteinander verbundene Konstrukte. Jedoch ist bis dato nicht abschließend geklärt, ob selektive Aufmerksamkeit für die perzeptuelle Integration von Objektelementen erforderlich ist. Die Ergebnisse vorhandener Studien sind nicht eindeutig: während einige Studien darauf hindeuten, dass selektive Aufmerksamkeit eine wichtige Rolle für Objektintegrationsprozesse spielt (z.B. Treisman & Gelade, 1980), behaupten andere, dass diese Prozesse präattentiv und automatisch ablaufen (Driver & Baylis, 1998; Gilchrist, Humphreys, & Riddoch, 1996; Scholl, 2001). Im zweiten Teil der vorliegenden Dissertation wurde daher die Rolle selektiver Aufmerksamkeit in Objektintegrationsprozessen genauer analysiert. Diese Fragestellung wurde anhand der Untersuchung aufmerksamkeitsgestörter Patienten, die einen lateralen Bias der räumlichen Aufmerksamkeit zeigen, angegangen. Insbesondere wurde im Rahmen einer visuellen Suchaufgabe geprüft, ob und in welchem Maße selektive Aufmerksamkeitsdefizite bei Patienten mit Extinktion zu Schwierigkeiten bei Objektintegrationsprozessen führen. Bei Darbietung eines Einzelreizes, der entweder einen zu gruppierenden Distraktor oder eine zu gruppierende Zielreiz Kanizsa Figur darstellte, zeigten Patienten keine signifikanten Unterschiede in der Suchleistung gegenüber gesunden Kontrollprobanden. In einer kompetitiven Suchsituation, in der mehrere zu gruppierende Objekte präsentiert wurden, zeigte sich dahingegen ein extinktionsspezifischer räumlicher Bias. Basierend auf diesen

Ergebnissen kann geschlussfolgert werden, dass in kompetitiven Suchsituationen ein Aufmerksamkeitsbias zu unausgewogenen Gruppierungsoperationen führt: intakte Gruppierung im rechten, beachteten, und eingeschränkte Gruppierung im linken, weniger beachteten Hemifeld. Dieses Ergebnis deutet auf einen wichtigen Beitrag selektiver Aufmerksamkeit zu Objektintegrationsprozessen hin.

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Gögler, N., Willacker, L., Funk, J., Strube, W., Langgartner, S., Napiórkowski, N., Hasan, A., & Finke, K. (2016). Single-session transcranial direct current stimulation induces enduring enhancement of visual processing speed in patients with major depression. *European Archives of Psychiatry and Clinical Neuroscience, 267*(7), 671-686.

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The author of this dissertation is the first author of this manuscript. JF, KF, NG and AH designed the study. NG and LW conducted the behavioural assessment. NG analysed the data. NN technically supported the TVA-fitting procedures. WS and SL recruited patients and applied tDCS. NG wrote the manuscript, which was commented on and revised by KF and AH.

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The author of this dissertation is the first author of this manuscript. JF, KF, HM, NG and AH designed the study. NG conducted the behavioural assessment and analysed the data. IP was responsible for the clinical ratings and recruitment of patients. TO-S, NF, and WS applied tDCS. NG wrote the manuscript, which was commented on and revised by KF and AH.

Study III:

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The author of this dissertation is the first author of this manuscript. MC and KF designed the study. MC programmed the experiment. IK recruited patients and provided the lesion maps. MC and NG analysed the data. MC, KF and NG wrote the manuscript; HM commented and revised the manuscript.

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