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Dopaminergic neuromodulation of semantic priming in a cortical network model

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ABSTRACT

Semantic priming between items stored and associated in memory underlies contextual recall. Response times to process a given target item are shorter when following presentation of a related prime item than when it is unrelated. The study of priming effects allows investigating the structure of semantic networks as a function of association strength and number of links relating the prime and target. Behavioral data from divided visual field experiments in healthy subjects show a variability in the magnitude of priming effects when the left or right hemisphere is primary involved. Data from schizophrenic patients also exhibit variability in priming magnitude compared to data from healthy subjects. Mathematical models of cortical networks allow theorists to understand the link between the physiology of single neurons and synapses and network behavior. Computational modelling can replicate electrophysiological recordings of cortical neurons in monkeys, that exhibit two types of task-related activity, 'retrospective' (related to a previously shown stimulus) and 'prospective' (related to a stimulus expected to appear, due to learned association between both stimuli). Experimental studies of associative priming report priming effects on behavioral data in both human and monkeys. Cortical network models can account for a large variety of priming effects observed in human, and for the dependence of retrospective activity on dopamine neuromodulation. Here, we investigate how variable levels of dopamine in a model of a cortical network can modulate prospective activity to vary the magnitude of semantic priming. We simulate a biologically realistic network of integrate and fire neurons to study the effects of dopaminergic neuromodulation of NMDA receptors of glutamatergic and gabaergic neurons on semantic priming dynamics. Results support the possibility that different levels of dopaminergic neuromodulation can subtend hemispheric differences in semantic priming, corresponding to focused priming in the left hemisphere and to extended priming in the right hemisphere. Furthermore, results can account for priming perturbations in schizophrenia depending on the level of dopamine.

1. Introduction

Semantic priming processes underlying contextual recall and language comprehension are reported to depend on learned associations between concepts in memory. The initial experimental study of semantic priming effects reported shorter response times to accept a target item as an actual word when related to a preceding prime (e.g., '*butter*' and '*bread*') than when unrelated (e.g., '*tree*' and '*bread*') (Meyer, Schvaneveldt, & Rudy, 1972; see Meyer & Schvaneveldt, 1971). According to the paradigm of mental chronometry, shorter reaction times are assumed to reflect dynamic 'activation' of the target word by a semantically related contextual prime word (see Hutchison, 2003; Neely, 1991 for reviews). The variability in priming effects is the object of numerous researches. Many data have revealed that priming magnitude depends on several cognitive parameters such as the strength and type of the prime-target relation (Brunel & Lavigne, in press; Chiarello, Liu, Shears, Quan, & Kacinik, 2003; Hutchison, 2003; Lucas, 2000; McRae, Cree, Seidenberg, & McNorgan, 2005; Neely, 1991 for reviews).

1.1. Semantic priming

Semantic priming effects can be tested according to different levels of association strength between prime and target, measured in production norms as the percentage of production of associates (targets) to a given word (prime) among several subjects (Cree & McRae, 2003; McRae, de Sa, & Seidenberg, 1997; Nelson, McEvoy, & Schreiber, 2004). Variable association strengths can be involved through a step1 relation between a prime and a target directly

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associated in memory (e.g., *tiger-stripes*). Step1 priming is typically reported to arise rapidly at short SOAs (stimulus onset asynchrony as the time elapsed between prime and target onsets) of a few tens of milliseconds (Hodgson, 1991; Lee, Binder, Kim, Pollatsek, & Rayner, 1999; Perea & Gotor, 1997; but see de Mornay Davies, 1998; Thompson-Schill, Kurtz, & Gabrieli, 1998). Variability in the magnitude of step1 priming effects is reported as depending on association strength *a* (Abernethy & Coney, 1993; Coney, 2002; Williams, 1996; see Hutchison, 2003, for a discussion). Priming effects are also reported through step2 relations between a prime and target indirectly associated through a common associate (e.g., *lion*-(tiger)-*stripes*) (Balota & Lorch, 1986; Bennett & McEvoy, 1999; Chwilla & Kolk, 2002; Kiefer, Weisbrod, Kern, Maier, & Spitzer, 1998; Kreher, Holcomb, & Kuperberg, 2006; Livesay & Burgess, 1998; McKoon & Ratcliff, 1992; McNamara & Altarriba, 1988; McNamara, 1992; Ratcliff & McKoon, 1988; Sayette, Hufford, & Thorson, 1996; Shelton & Martin, 1992; Spitzer, Braun, Hermle, & Maier, 1993a; Spitzer, Braun, Maier, Hermle, & Maher, 1993b; Weisbrod, Maier, Harig, Himmelsbach, & Spitzer, 1998; but see Chwilla, Kolk, & Mulder, 2000; de Groot, 1983). Step2 priming is reported as weaker than step1 priming (Arnott, Chenery, Copland, Murdoch, & Silburn, 2003; Hill, Strube, Roesch-Ely, & Weisbrod, 2002; Kiefer, Ahlegian, & Spitzer, 2005; McNamara, 1992; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2002; Rossell, Rabe-Hesketh, Shapleske, & David, 2000).

The variability of the magnitude of priming effects is greater at short SOAs depending on associations strength (Abernethy & Coney, 1993; Coney, 2002) and step (Bennett & McEvoy, 1999; Hill et al., 2002; Kiefer et al., 2005; Kischka et al., 1996; Moritz et al., 1999; Spitzer et al., 1993a; Spitzer et al., 1993b; see Brunel & Lavigne, in press, for a review). This variability allows to investigate the different patterns of priming as a function of hemispheric processing and their pathological perturbations.

1.2. Hemispheric priming

An important factor reported as influencing the mode of semantic processing is the cerebral hemisphere primarily involved. Divided visual field experiments investigate the relative magnitudes of semantic priming effects when the prime and/or target are presented in the right visual field-left hemisphere (RVF-LH) or in the left visual field-right hemisphere (LVF-RH) (e.g., Brunel & Lavigne, in press; Chiarello et al., 2003 for reviews). Behavioral data reported at short SOAs show that step1 priming arises when the RVF-LH is involved (Bouaffre & Faita-Ainseba, 2007) and when both hemispheres are involved (Frishkoff, 2007; Hutchinson, Whitman, Abeare, & Raiter, 2003). In the later case priming of weak associates is weaker than priming of strong associates (Coney, 2002; Frishkoff, 2007). The LVF-RH exhibits priming of strong associates (Hutchinson et al., 2003; but see Nakagawa, 1991) and of weak associates (Hutchinson et al., 2003), while the RVF-LH exhibits priming of strong associates only (Abernethy & Coney, 1993; Coney, 2002; Nakagawa, 1991; Yochim, Kender, Abeare, Gustafson, & Whitman, 2005). Step2 priming is reported at short SOAs as smaller than step1 priming when both hemispheres are involved (Kiefer et al., 1998; Yochim et al., 2005; see Richards & Chiarello, 1995 for RH effects when primes are centrally presented). It is less reliable when only one hemisphere is involved (Yochim et al., 2005). Hemispheric differences in semantic priming effects have been described as 'fine' or focused semantic coding in the left hemisphere, in which strong step1 associates are activated, and 'coarse' or extended semantic coding in the right hemisphere, in which strong and weak step1 and step2 associates are activated (Beeman, Bowden, & Gernsbacher, 2000; Beeman & Chiarello, 1998; Beeman, Friedman, Grafman, & Perez, 1994; Chiarello et al., 2003). On the one hand, the synaptic hypothesis proposes that hemispheric differences in semantic processing depend on different synaptic properties of the left and right networks (Jung-Beeman, 2005; see Brunel & Lavigne, in press, for a modeling approach). On the other hand, the neuromodulatory hypothesis proposes that differential dopaminergic modulation could be involved in the two hemispheres, according to studies reporting different levels of dopamine (Slopsema, van der Gugten, & de Bruin, 1982) and different impacts of dopamine agonist in the left and right hemispheres (Roesch-Ely et al., 2006). Then, the question remains open as to if and how dopamine can actually modulate the magnitude of step1 and step2 semantic priming.

1.3. Priming in schizophrenia

Schizophrenic patients are reported to exhibit unbalanced hemispheric lateralization as well as perturbed semantic priming (Manschreck et al., 1988; Moritz et al., 2001, 2002; Rossell & David, 2006; Spitzer et al., 1993a,b). Dysfunctional dopamine neuromodulation is proposed as involved in the modifications of the magnitude of priming effects in schizophrenia (Abi-Dargham et al., 2002; Kischka et al., 1996; Roesch-Ely et al., 2006). Data suggest that the magnitudes of direct step1 and indirect step2 priming are differentially affected in some schizophrenic patients, depending on the time course of priming effects across variable SOAs.

When considering behavioral reaction time data at long SOAs, decreased (Barch et al., 1996; Besche et al., 1997) or increased (Gouzoulis-Mayfrank et al., 2003; Lecardeur et al., 2007) priming effects are reported in schizophrenic patients. SOAs longer than 450 ms are considered as involving various types of priming processes such as association-based activation and slow facilitatory or inhibitory expectancies (Deacon, Uhm, Ritter, Hewitt, & Dynowska, 1999; Neely, 1976, 1991). The global priming effect reported at long SOAs is then the end-product of complex interacting processes difficult to disentangle and interpret (Keefe & Neely, 1990; Neely, 1991; Neely, Keefe, & Ross, 1989). In addition, differences between patients and controls on ERPs data are not significant at long SOAs though arising at short SOAs (Kreher, Holcomb, Goff, & Kuperberg, 2007). Short SOAs are considered as involving solely automatic priming processes that can be interpreted in a more straightforward way as automatic spreading of activation from the prime to the related target (Keefe & Neely, 1990; Neely et al., 1989). When compared to priming effects in healthy subjects, reported effects in schizophrenic patients at short SOAs exhibit a great variability, ranging from hypo-priming (Henik, Priel, & Umansky, 1992; Ober, Vinogradov, & Shenaut, 1997) to hyper-priming (Babin, Wassef, & Sereno, 2007; Lecardeur et al., 2007; Manschreck et al., 1988; Moritz et al., 2001, 2002; Spitzer et al., 1993a, 1994; Weisbrod et al., 1998), with the possibility for normal priming (Barch et al., 1996; see Minzenberg, Ober, & Vinogradov, 2002 for a review). Hyper-priming is also reported as more reliable, or of larger magnitude, for step2 than step1 relations (Kreher et al., 2007; Manschreck et al., 1988; Moritz et al., 2002; Spitzer et al., 1993a,b).

Numerous data on the effects of dopamine on working memory have led researchers to interpret variations in the magnitude of priming as caused by perturbations of dopamine neuromodulation in schizophrenia (Kischka et al., 1996; Spitzer et al., 1993a). To test for this hypothesis, double blind studies investigated the effects of precursors of DA receptors agonists compared to placebo in healthy subjects. Reported effects mirrored hyper-priming reported in schizophrenic patients. Step2 but not step1 priming is reduced under L-Dopa (amino acid L-3,4-dihydroxyphenylalanine, unselective agonist) compared to placebo (Angwin, Chenery, Copland, Murdoch, & Silburn, 2004; Copland, Chenery, Murdoch, Arnott, & Silburn, 2003; Kischka et al., 1996), and step2 priming only is reduced in the RVF-LH under pergolide (unselective D1/D2 recep-

tors agonist) compared to placebo and to bromocriptine (selective D2 receptors agonist) (Roesch-Ely et al., 2006). The magnitude of priming effects in healthy subjects then depend on the ingestion of dopamine precursor. However, it is still unknown if dopamine modulates priming effect by acting at the cortical level where semantic processes are assumed to occur. In addition, increased priming effects are reported on schizophrenic patients exhibiting formal thought disorders but not on other schizophrenic patients (Moritz et al., 2001, 2002; Spitzer et al., 1993a), which raises the question of the possible involvement of a precise level of dopamine depletion on the pattern of priming.

Though the effects of dopamine on semantic priming *per se* have been seldom studied, perturbed levels of dopamine are considered as subtending disorders associated to schizophrenia (Abi-Dargham et al., 2002; Abi-Dargham & Moore, 2003; Fleming, Goldberg, Gold, & Weinberger, 1995; Gooding & Tallent, 2004; Park & Holzman, 1992; Park & Holzman, 1993a; Park & Holzman, 1993b). Dopamine is considered to be a key factor in working memory functions (Arnsten, 1998; Tanaka, 2006). Indeed, depletion of dopamine (Brozoski, Brown, Rosvold, & Goldman, 1979) or infusions of D1 receptors (D1R) antagonists (Sawaguchi & Goldman-Rakic, 1991) into the prefrontal cortex (PFC) severely impairs working memory performance. Both electrophysiological and behavioral studies report that the dependence of mnemonic activity on dopamine modulation follows a bell-shaped curve (Arnsten, 1998; Murphy, Arnsten, Jentsch, & Roth, 1996; Williams & Goldman-Rakic, 1995; Zahrt, Taylor, Mathew, & Arnsten, 1997). Amphetamine improves working memory performance of schizophrenic patients (Daniel et al., 1991), suggesting that the PFC of schizophrenic patients is in a hypodopaminergic state (Davis, Kahn, Ko, & Davidson, 1991). The assumption that it is due to D1R disorganization or depletion in the PF, cingulate and temporal cortices, is supported by receptor imaging studies (Okubo, Suhara, Suzuki, & Kobayashi, 1997; see Abi-Dargham et al., 2002; Abi-Dargham & Moore, 2003) and by electrophysiological studies (Williams & Goldman-Rakic, 1995). In addition, schizophrenic patients present aberrant brain lateralization (Bracha, 1987; Lyon and Satz, 1991) as well as modified asymmetry of cerebral anatomy (Crow, Colter, Frith, Johnstone, & Owens, 1989; Petty, 1999; Raz et al., 1987) and dopamine neurotransmission (Hietala et al., 1999). Differential dopamine neuromodulation could be involved not only between healthy participants and schizophrenic patients, but also between the left and right hemispheres. Indeed, in healthy subjects, L-dopa has differential effects on the lateralization of lexical processing depending on their schizotypal features (Mohr et al., 2005) and on the relative magnitudes of semantic priming in the right and left hemispheres (Roesch-Ely et al., 2006). Lateralization of normal cerebral functions might then be related to an underlying lateralization of the net effect of dopamine on cortical neurons (see Vernaleken et al., 2007). Then, the test for the effects of dopamine on semantic priming at the behavioral level requires taking into account of dopamine effects at the cellular level.

1.4. Dopamine neuromodulation at the cellular level

Neurophysiological observations of dopaminergic afferences on both excitatory and inhibitory neurons (Sesack, Bressler, & Lewis, 1995; Sesack, Hawrylak, Melchitzky, & Lewis, 1998; Verney, Alvarez, Geffard, & Berger, 1990; Williams & Goldman-Rakic, 1993) suggest that dopamine could modulate both excitatory and inhibitory transmission. Regarding excitatory pyramidal neurons, D1R stimulation is reported as reducing inhibitory post-synaptic currents (IPSCs; Seamans, Gorelova, Durstewitz, & Yang, 2001; Trantham-Davidson, Neely, Lavin, & Seamans, 2004; but see Gao & Goldman-Rakic, 2003; Gao, Krimer, & Goldman-Rakic, 2001) and increasing spontaneous excitatory post-synaptic currents (EPSC; Wang, Feng, & Zheng, 2002). The modulation of membrane excitability, by increased D1R activation, increases the number of spikes (Kroner, Krimer, Lewis, & Barrionuevo, 2007; Tseng, Lewis, Lipska, & O'Donnell, 2007) and enhances peak NMDA currents of 30% in a concentration-dependent fashion (Flores-Hernandez et al., 2002). D1R activation may then boost incoming weak synaptic inputs and increase responsiveness of pyramidal neurons to NMDA-mediated synaptic responses (Cepeda, Colwell, Itri, Chandler, & Levine, 1998; Galarraga, Hernandez-Lopez, Reyes, Barral, & Bargas, 1997; Hernandez-Lopez, Bargas, Surmeier, Reyes, & Galarraga, 1997; Seamans et al., 2001; Wang & O'Donnell, 2001; Young & Yang, 2004). D1R activation then enhances PFC cell excitability (Henze, Gonzalez-Burgos, Urban, Lewis, & Barrionuevo, 2000; Lavin & Grace, 2001; Seamans & Yang, 2004; Yang & Seamans, 1996) at least at prolonged times after dopamine agonist application (Rotaru, Lewis, & Gonzalez-Burgos, 2007). Regarding inhibitory interneurons, D1R activation is reported as increasing excitability of fast spiking interneurons (Gao & Goldman-Rakic, 2003; Gorelova, Seamans, & Yang, 2002; Kroner et al., 2007; Zhou & Hablitz, 1999; see also Tseng & O'Donnell, 2004), the FS-P type of synapses representing 98% of interneuron-pyramidal synapses (Gao & Goldman-Rakic, 2003). D1 receptors are reported as more abundant in the PFC than D2 receptors as (Farde et al., 1987; Goldman-Rakic, Lidow, & Gallager, 1990; Lidow, Goldman-Rakic, Gallager, & Rakic, 1991; see Muly, Szigeti, & Goldman-Rakic, 1998), D2 activation having varying effects on interneurons (Gorelova et al., 2002; Seamans et al., 2001; Trantham-Davidson et al., 2004; Tseng & O'Donnell, 2004; Wang et al., 2002). D1 receptors are considered as essential to working memory function in the PFC (Bandyopadhyay & Hablitz, 2007; Muller, von Cramon, & Pollmann, 1998; Murphy et al., 1996; Sawaguchi & Goldman-Rakic, 1991; Sawaguchi & Goldman-Rakic, 1994; Williams & Goldman-Rakic, 1995), by neuromodulating the gain within the PFC network (Seamans & Yang, 2004). D1R activation increases NMDAR-based excitatory synaptic transmission (Cepeda, Radisavljevic, Peacock, Levine, & Buchwald, 1992; Zheng, Zhang, Bunney, & Shi, 1999; see Bandyopadhyay, Gonzalez-Islas, & Hablitz, 2005) and inhibitory synaptic transmission (Gellman & Aghajanian, 1993; Penit-Soria, Audinat, & Crepel, 1987; Zhou & Hablitz, 1999; but see Law-Tho, Hirsch, & Crepel, 1994). This would enable dopamine to modulate cortical networks by decreasing the amplitude, duration and spread of activity among cortical neurons (Bandyopadhyay & Hablitz, 2007). Indeed, Williams and Millar (1990) have shown that excitation is increased at low levels of dopamine, whereas inhibition dominates at higher levels. A possible underlying mechanism could rely on the fact that NMDAR channels on pyramidal cells and interneurons express different sensitivities to dopamine levels (Muly et al., 1998). The authors proposed that for increasing levels of dopamine, pyramidal neurons begin increasing their response, and reach maximum response, at lower concentrations than interneurons. This raises the possibility of a differential effect of dopamine on NMDAR conductances of pyramidal neurons and interneurons (Brunel & Wang, 2001). Data on the effects of dopamine at the cellular level must then be linked to data on the cellular correlates of semantic priming at the behavioral level.

1.5. Priming in monkeys

Electrophysiological recording of cortical neurons of monkeys is the only way to probe the dynamics of neuronal activity at the cellular level. Neurons firing rates can be correlated to priming in monkeys performing pair associate tasks whose protocols are very similar to those used in human priming studies (Brunel & Lavigne, in press). In such tasks, a 'prime' image is first shown, followed after

a delay period by a 'target' image. During the delay period, neurons selective for the prime exhibit retrospective activity, that is they maintain an elevated firing rate following presentation of the prime (Fuster & Alexander, 1971; Miyashita, 1988; Miyashita & Chang, 1988), assumed to subtend short-term or working memory of a stimulus after its removal. In addition, neurons selective for a target associated to the presented prime exhibit prospective activity, that is their firing rate increases during the delay period following a prime (Erickson & Desimone, 1999; Fuster, 2001; Miyashita, 1988; Miyashita & Chang, 1988; Naya, Yoshida, & Miyashita, 2001; Naya, Yoshida, & Miyashita, 2003a; Naya, Yoshida, Takeda, Fujimichi, & Miyashita, 2003b; Rainer, Rao, & Miller, 1999; Sakai & Miyashita, 1991; Yoshida, Naya, & Miyashita, 2003). Those populations of neurons activated before the actual presentation of the target could correspond to the pre-lexical and anticipatory activation of the target corresponding to automatic priming in humans. Indeed, priming-like effects are reported in monkeys, with shorter reaction times on targets associated to the preceding prime than on target not associated (e.g., Erickson & Desimone, 1999). In addition, spike rates of neurons coding for a given item are reported to predict behavioral data such as reaction time on this item (Roitman & Shadlen, 2002). Understanding of individual neurons dynamics during semantic priming involves understanding the dynamics of whole networks of neurons connected together with varying synaptic strengths between the prime and target.

1.6. Computational models

Theoretical modeling allows relating network processes at the cellular level to emerging properties of priming effects observed at the behavioral level. Abstract 'connectionist' models are able to account for some of the priming effects reported in humans (Anderson, 1976, 1983; Becker, Moscovitch, Behrmann, & Joordens, 1997; Collins & Loftus, 1975; Collins & Quillian, 1969; Cree & McRae, 2003; Cree, McRae, & McNorgan, 1999; Masson, Besner, & Humphreys, 1991; Moss, Hare, Day, & Tyler, 1994; Plaut, 1995; Plaut & Booth, 2000; Quillian, 1967; Randall, Moss, Rodd, Greer, & Tyler, 2004; Sharkey & Sharkey, 1992). However these models do not account for behavioral data in terms of biologically realistic neurons dynamics and network architecture, which prevents simulation of the neuromodulation on the network behavior. Computational models of cortical networks are proposed to account for the monkey neurophysiological data based on realistic properties of neurons (Amit, 1995; Brunel, 1996, 2004; Wang, 2002). They account both for retrospective activity in working memory (Amit, Bernacchia, & Yakovlev, 2003; Amit & Brunel, 1997; Brunel & Wang, 2001; Haarmann & Usher, 2001; Renart, Moreno, de la Rocha, Parga, & Rolls, 2001) and prospective activity in paired associate tasks (Brunel, 1996; Lavigne, 2004; Lavigne & Denis, 2001; Lavigne & Denis, 2002; Mongillo, Amit, & Brunel, 2003). A recent approach allowed modeling a large variety of priming effects reported in human within the common framework of a model of a cortical network (Brunel & Lavigne, in press). The synaptic hypothesis tested by the authors have shown that variable synaptic strengths can account for the variability in priming effects observed between the cerebral hemispheres and between healthy and schizophrenic subjects. However the dependence of priming on the widely evoked dopamine neuromodulation is still to be tested. Cortical networks models allow testing for the effects of neuromodulation on retrospective activity in working memory. In computational studies, simulations of D1R activation show an increase of the resistance of retrospective activity to distractors (Brunel & Wang, 2001; Durstewitz, Kroner, & Gunturkun, 1999; Durstewitz & Seamans, 2002; Durstewitz, Seamans, & Sejnowski, 2000; Tanaka, 2002, 2006; Wang, 2006; Yamashita & Tanaka, 2002; Yamashita & Tanaka, 2003). Furthermore, Brunel and Wang (2001) tested for the effect of D1R activation on the differential neuromodulation of NMDA receptors on glutamatergic and gabaergic neurons (Muly et al., 1998). The increase of the gain in membrane conductance was larger for pyramidal neurons at low levels of D1R activation, and larger for interneurons at high levels of D1R activation. Their results show that for intermediate values of D1R activation where the gain difference between pyramidal and interneurons is the largest, there is a window of increased signal-to-noise ratio leading to a bell-shaped curve for the dependence of retrospective activity on D1R activation (Arnsten, 1998; Williams & Goldman-Rakic, 1995). Computational models then support the hypothesis that the activation of D1 receptors changes the balance between the excitation and the inhibition in cortical networks (Goldman-Rakic, Muly, & Williams, 2000; Muly et al., 1998) to increase the signal-to-noise ratio (Cohen & Servan-Schreiber, 1992; Winterer, Coppola, Egan, Goldberg, & Weinberger, 2003). Then, with respect to known data on the effects of dopamine on cortical neurons at the cellular level, cortical network models can account for the dependence of retrospective activity on D1R activation. Computational models are then good candidates to investigate the effects of dopamine neuromodulation on prospective activity involved in semantic priming. The main goal of the present research is then to investigate to what extent biologically realistic cortical networks models can account for dopamine neuromodulation of the magnitude of semantic priming. Such models have been successful in reproducing both electrophysiological data in monkey and a wide variety of behavioral findings on priming in human depending on synaptic strengths. However, the neuromodulatory hypothesis is still to be investigated in a modeling approach to test for a link between dopamine and priming effects in the cerebral hemispheres and in schizophrenia.

2. Materials and methods

We simulated a large-scale model of integrate and fire neurons for two main reasons. First, it allows us to implement separately synaptic currents induced by different receptors, i.e., AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (*N*-methyl-D-aspartate) glutamate receptors, and $GABA_A$ (γ-aminobutyric acid) receptors, allowing investigating the effects of dopaminergic modulation on network behavior. Second, we can implement realistic sources of noise leading to trial-to-trial variability, which enables to test for the statistical significance of priming effects as a function of modulated signal-to-noise ratio.

The model is composed of N_E excitatory pyramidal cells and N_I inhibitory inter-neurons, with $N_I = 0.25N_E$ (Abeles, 1991; Braitenberg & Schütz, 1991) with a probability of $C = 0.2$ of having a synapse from any pre-synaptic neuron to any post-synaptic neuron (Fig. 1A). Neurons are connected through four types of synapses. Synaptic efficacies involving inhibitory neurons, excitatory to inhibitory (IE), inhibitory to excitatory (EI), inhibitory to inhibitory (II), are not subject to variation due to learning. Excitatory and inhibitory neurons receive external noise from other cortical areas, obeying a Poisson process of rate ν_{ext} leading to realistic values of mean neurons activity of 3 Hz for excitatory neurons and 9 Hz for inhibitory interneurons (Burns & Webb, 1976; Koch & Fuster, 1989; Wilson & Goldman-Rakic, 1994). Inhibitory interneurons are activated by excitatory neurons to prevent runaway propagation of activation and regulate populations dynamics in the network. Excitatory neurons encode p items, each item corresponding to a low fraction $f \ll 1$ of the total N_E excitatory neurons. Synapses between neurons coding for a same item are potentiated at J_1, synapses between neurons coding different and non-associated items are depressed at J_0, and synapses between different and associated items are potentiated at J_a.

Neurons of the network are leaky integrate-and-fire (IF) neurons (Tuckwell, 1988). The state of a neuron is described by its depolarization $V(t)$ (mV) obeying the following equation:

$$\tau_m \frac{dV(t)}{dt} = -V(t) + I(t) \quad (1)$$

where τ_m is the membrane time constant of excitatory cells ($\tau_E = 20$ ms) and inhibitory cells ($\tau_I = 10$ ms) (McCormick, Steinmetz, & Thompson, 1985). $I(t)$ is the total afferent synaptic current (in units of V) due to spikes arriving from presynaptic neurons. When $V(t)$ reaches a threshold θ, the neuron emits a spike and V is reset to V_τ, following a refractory period τ_{RP}. The total synaptic current I is the sum of receptor-dependent currents evolving with their own dynamics and due to recurrent excitatory and inhibitory activities, external noise and

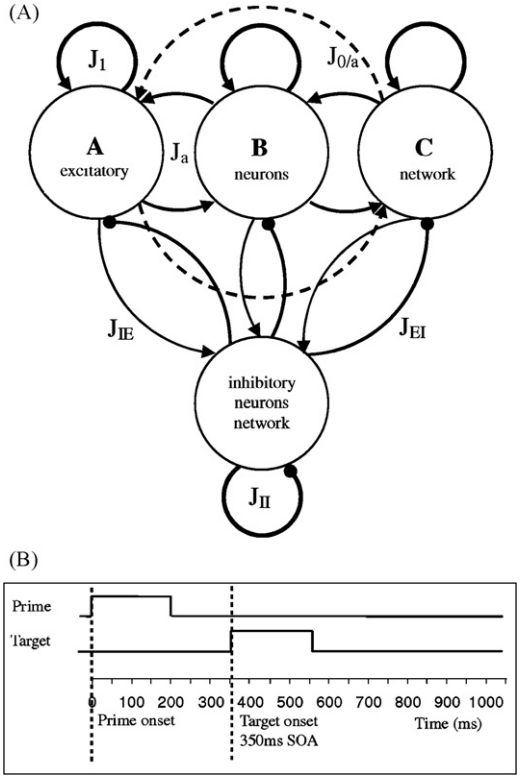

Fig. 1. (A) Architecture of the excitatory-inhibitory network: excitatory neurons are divided in p subpopulations of neurons selective for distinct stimuli. Inhibitory neurons are non-selective. (B) Protocol presenting trials with 350 ms SOAs used in priming simulations: spontaneous activity for 50 ms, prime input for 200 ms, delay (inter-stimuli interval, ISI for 150 ms), target input for 200 ms and post-target delay for 50 ms.

input stimuli (Eq. (2)):

$$I = gxI_{\text{NMDA rec}} + (1-x)I_{\text{AMPA rec}} + I_{\text{GABA rec}} + (1-x+\lambda)\,I_{\text{AMPA ext}} \tag{2}$$

where x, $(1-x)$, is the fraction of excitatory currents induced by NMDARs (AMPARs), and I_{GABA} the current induced by $GABA_A$Rs. I_{ext} is the external current induced by noise which we assume to be induced by AMPARs only. λ is the contrast of the external afferent input over external noise, equal to 0 when no input is presented to the network and 0.1 for a given neurons population when the neuron receives selective afferents when the specific item is presented to the network with a rate $\lambda\nu_{\text{ext}}$ (Mongillo et al., 2003). g is the gain of excitatory currents induced by NMDAR of glutamatergic and gabaergic neurons, differentially modulated by dopamine activation of D1R, according to Eq. (3) (see Fig. 3A):

$$g_{\text{NMDA}} = 1 + \frac{r}{1+\exp(n - D_1/0.25)} \tag{3}$$

where D_1 is the level of D1R activation by dopamine, $r = 0.3$ is the ratio of neuromodulation of the gain of NMDARs induced excitatory currents, and $n_{\text{glu}} = 0.8$ and $n_{\text{GABA}} = 1.2$ are the factors of differential neuromodulation of glutamatergic and gabaergic neurons NMDAR currents, respectively.

Individual excitatory and inhibitory post-synaptic currents I_s obey the Eq. (4):

$$\tau_s \frac{dI_s(t)}{dt} = -I_s(t) + \tau_m J \sum_k \delta(t - t_k - \delta_s) \tag{4}$$

where J is the synaptic efficacy (mV) corresponding to the total charge transmitted across the synapse by a single spike described as an instantaneous current injection. δ_s is the synaptic delay and t_k the time of synaptic activation due to the kth spike. Upon the emission of a presynaptic spike, the post-synaptic current has, following a delay δ_s specific to the type of excitatory or inhibitory neuron, an instantaneous jump proportional to the efficacy J, followed by a an exponential decay with time constant τ_s. Different τ_s account for the different receptors involved (Hestrin, Sah, & Nicoll, 1990; Salin & Prince, 1996; Spruston, Jonas, & Sakmann, 1995; Xiang, Huguenard, & Prince, 1998): AMPARs (fast activation and decay, $\tau_{\text{AMPA}} = 2$ ms), NMDARs (slow activation and decay, $\tau_{\text{NMDA}} = 100$ ms) and GABARs (fast activation and decay, $\tau_{\text{GABA}} = 2$ ms).

2.1. Scenarios of semantic structures of stimuli and associated synaptic matrix

10 items are encoded within the network by 10 populations of neurons. Neurons coding for unrelated, same, and related items are associated with synapses of value J_0, J_1, and $J_a = J_0 + a(J_1 - J_0)$, respectively. Synaptic connectivity embeds various types of prime-target relations according to matrix 5, with a taking values a', b' and c'. For clarity 0, 1, a', b' and c' account for J_0, J_1, and $J_{a'}$, $J_{b'}$ and $J_{c'}$, respectively:

$$M = \begin{bmatrix} 1 & b' & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ b' & 1 & b' & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b' & 1 & b' & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & b' & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & a' & c' & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a' & 1 & 0 & b' & 0 & 0 \\ 0 & 0 & 0 & 0 & c' & 0 & 1 & 0 & b' & 0 \\ 0 & 0 & 0 & 0 & 0 & b' & 0 & 1 & 0 & b \\ 0 & 0 & 0 & 0 & 0 & 0 & b' & 0 & 1 & b' \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & b' & b' & 1 \end{bmatrix} \tag{5}$$

Such a synaptic matrix enables to test for: step1 priming as a function of association strength on target 6 (strong associate; $a' = 0.8$) and 7 (weak associate; $c' = 0.5$) following related prime 5 and on target 9 (medium associate; $b' = 0.7$) following related prime 10 vs. unrelated prime 1 (Fig. 2); step2 priming on target 3 following related prime 1 vs. unrelated prime 5 ($a' = 0.7$; Fig. 3). A total of 220 simulation trials were run on the following 22 inter-trial conditions: with regard to step1 priming: 2 prime-target relatedness (related vs. unrelated) $\times 3$ association strength ($a' = 0.8$ vs. $b' = 0.7$ vs. $c' = 0.5$) $\times 2$ levels of D_1 of D1R activation (1 vs. 1.5); with regard to step2 priming: 2 prime-target relatedness (related vs. unrelated) $\times 5$ levels D_1 (0 vs. 0.5 vs. 1 vs. 1.5 vs. 2). Such a synaptic structure is heterogeneous, which makes it realistic with regard to experimental conditions where variable numbers of associated items and association strengths are likely to be present. Model parameters are given in Table 1.

Each cycle in the network ($dt = 0.1$ ms $\ll \tau$) consists in updating spikes receptions and discharges for every neuron, and computing spike rates of neurons populations (10 ms bins). The 220 simulation trials were computed at a mean speed of 3 ms per second on a 3 GHz PIV computer.

2.2. Protocol

Experimental protocols used in humans are emulated in the cortical network model to investigate the variety of priming effects in terms of neurons populations dynamics. Priming effects are tested according to experimental protocol displayed in Fig. 1B: first 200 ms without any input (the last 50 ms are displayed); then the prime was displayed for $t_1 = 200$ ms, followed by a delay periods $t_d = 150$ ms with no selective input (inter-stimuli interval, ISI), which defined a stimulus onset asynchrony of 350 ms (SOA = $t_1 + t_d$); finally the target was displayed for 200 ms, followed by 50 ms with no input before the end of trial. A trial begins with the network in a state of spontaneous activity. When the prime is displayed, the corresponding neurons population reaches an elevated activity ('visual response'). After prime removal, the excitatory connectivity is strong enough so that these neurons do not come back to spontaneous activity, but rather exhibit retrospective persistent activity. The elevated activity of such neurons leads in turn to activation of populations of neurons coding for related stimuli. Hence, at the time of the presentation of the target, neuronal populations that code for associated step1 and step2 targets exhibit increased firing rates corresponding to prospective activity. Recognition or response times to a given item are usually computed as proportional to its level of activation in memory (Bullinaria, 1995; Masson, 1995; Masson et al., 1991; Plaut, 1995; Plaut & Booth, 2000; Randall et al., 2004). Electrophysiological studies have reported that spike rates of neurons coding for a given response are negatively correlated to response times (Roitman & Shadlen, 2002). Based on this experimental data, many modeling approaches in cortical networks take the reaction time to be the time at which the mean spike rate of a population of neurons reaches a prescribed threshold (Brunel & Lavigne, in press; Wang, 2002; Wong & Wang, 2006), similar to classical diffusion models of reaction time (Ratcliff, 1978). Then, when a target is displayed to the cortical network, its recognition time T^θ is the time elapsed from target onset to the instant at which the mean firing rate of the corresponding neurons population rises for the first time above a threshold ν^θ. For a given target, T^θ depends on the level of prospective activity of the neurons population coding for this target at target onset, itself assumed to depend on the synaptic matrix and preceding prime. The target can follow a related (R), unrelated (U) or no (neutral, N) prime, leading to specific recognition times T^θ_R, T^θ_U and T^θ_N, respectively. These response times enable to quantify the activatory (Eq. (6)) and inhibitory (Eq. (7)) components of priming effects (Eq. (8)):

$$\text{PE}_{\text{act}} = T^\theta_N - T^\theta_R \tag{6}$$

$$\text{PE}_{\text{inh}} = T^\theta_N - T^\theta_U \tag{7}$$

with the global priming effect calculated as:

$$\text{PE} = \text{PE}_{\text{act}} - \text{PE}_{\text{inh}} \tag{8}$$

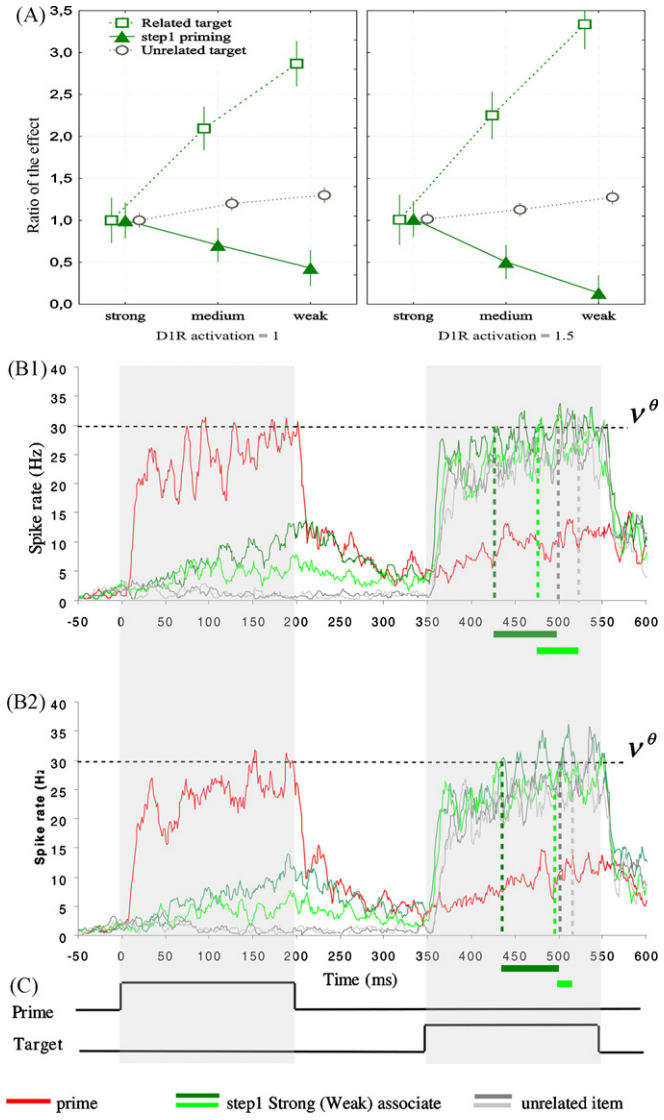

Fig. 2. Effects of neuromodulation on Step1 priming effects (see Fig. 3A for differential neuromodulation of the gain g of NMDARs conductances by D1R activation). (A) Neuromodulation of the magnitude of Step1 priming effects for relevant values of D1R activation $D_1 = 1$ and $D_1 = 1.5$, as a function association strength a. Relative magnitudes of Step1 priming of strong ($a' = 0.8$), medium ($b' = 0.7$) and weak ($c' = 0.5$) associates (green triangles), as difference between response times in the unrelated (gray circles) and related (green squares) conditions, are calculated as ratios of priming in each condition of D1R activation and association strength over mean value of priming of strong associates for $D_1 = 1$. Step1 priming increases with association strength ($p < 0.05$). Step1 priming does not depend on D1R activation and the effect of strength is significant for $D_1 = 1.5$ ($p < 0.01$) but not for $D_1 = 1$ (*ns*). The effect of D_1 activation on priming of weak step1 associate is due to variations in response times on related target (green squares; $p < 0.01$) but not to variations in response times on unrelated targets (gray circles; *ns*). (B1–2) Representative trials showing populations spike rates for weak and strong associates as a function of time for $D_1 = 1$ and 1.5, respectively, according to the protocol C (see Fig. 1B). Priming effects are indicated by the difference between dark (light) green (strong or weak associate) and dark (light) gray (same items but unrelated) spotted vertical lines that indicate trial averaged time from target onset for targets population activity to reach over-threshold activity $\nu^\theta = 30$ Hz. Horizontal dark (light) green bars indicate trial averaged magnitude of Step1 priming effects on strong (weak) associates modulated by D1R activation ($D_1 = 1$ and 1.5) due to modification of reaction times in the related condition ($T^\theta_{\text{R strong}} = 123$ and 131; $T^\theta_{\text{R weak}} = 175$ and 198; $p < 0.5$) but not in the unrelated condition ($T^\theta_{\text{U strong}} = 204$ and 190; $T^\theta_{\text{U weak}} = 222$ and 218; *ns*) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

Table 1
Parameters of the model of IF neurons

N_E	Number of excitatory neurons	4000
N_I	Number of inhibitory neurons	1000
C	Connectivity	0.2
C_E	Number of recurrent excitatory, Connections per neuron	800
C_{ext}	Number of external excitatory, Connections per neuron	2200
C_I	Number of recurrent inhibitory, Connections per neuron	200
p	Number of items	10
N_{Ep}	Number of neurons per item	400
f	Coding level	N_{Ep}/N_E
τ_{mE}	Membrane time constant, excitatory neurons	20 ms
τ_{mI}	Membrane time constant, inhibitory neurons	10 ms
ν^θ	Firing threshold, both types	20 mV
$V_{\tau E}$	Reset membrane potential, excitatory neurons	10 mV
$V_{\tau I}$	Reset membrane potential, inhibitory neurons	15 mV
τ_{RP}	Refractory period, both types	2 ms
J_{EE}	Average E → E efficacy	0.05 mV
J_{IE}	E → I efficacy	0.1 mV
J_{EI}	I → E efficacy	0.3 mV
J_{II}	I → I efficacy	0.5 mV
J_{Eext}	External E → E efficacy	0.052 mV
J_{Iext}	External E → I efficacy	0.1 mV
J_1	Potentiated E → E efficacy between neurons coding for a same item	0.095
a	Association strength, between associated items	$a' = 0.5$, $b' = 0.7$, $c' = 0.8$
J_a	Potentiated E → E efficacy between associated items	$J_0 + a(J_1 - J_0)$
J_0	Depressed E → E efficacy between non-associated items	$(J_{EE} - fJ_1)/(1 - f)$
τ_{AMPA}	Synaptic decay type, AMPA-R	2 ms
τ_{NMDA}	Synaptic decay type, NMDA-R	100 ms
τ_{GABA}	Synaptic decay type, GABA-R	5 ms
x	Fraction of NMDA currents	0.3
D_1	Activation of D_1 receptors to DA	0, 0.5, 1, 1.5, 2
g	Gain of NMDA-R conductances of glutamatergic and gabaergic neurons	See Eq. (3)
δ_E	Latency (transmission delay), excitatory neurons	15–30 ms
δ_I	Latency (transmission delay), inhibitory neurons	0.5 ms
ν_{ext}	External Poisson noise	15 Hz
λ	Contrast of external input	0.1
ν^θ	Threshold for reaction time	30 Hz

3. Results

During the delay period following prime presentation to the network, neurons coding for the prime exhibit retrospective activity while neurons coding for associated items exhibit prospective activity. Several neurons populations are activated simultaneously in the network's working memory (Amit et al., 2003; Brunel, 1996; Haarmann & Usher, 2001; Lavigne, 2004), allowing the network to activate step1 and step2 associates. Because of the increased connection strength (as measured by the parameter a) between that population and the populations coding for associated stimuli, these populations have enhanced firing rates compared to baseline. Hence, when the second stimulus shown is associated to the first through step1 and step2 associations, the corresponding population has initially a higher firing rate than if the first stimulus had not been shown. It then reaches the threshold for recognition ν^θ faster than an unrelated target. Differences in the response times exhibited by the network correspond to priming effects. Simulations were performed for different prime-target pairs based on synaptic matrix (5). In the simulations, the firing rates of neurons populations coding for items not relevant for a given scenario remain at the level of spontaneous activity. For clarity, those as well as firing rates of inhibitory neurons, are not displayed in figures.

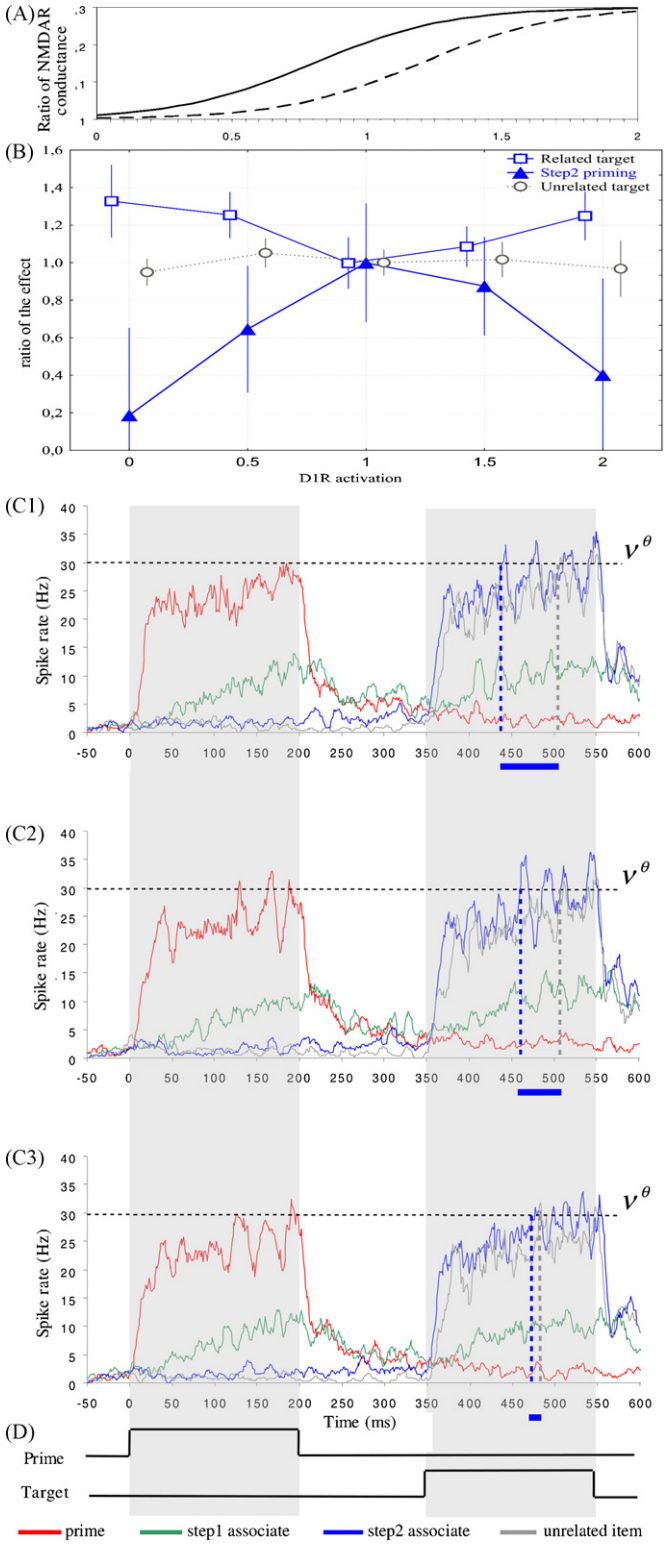

Fig. 3. Effects of neuromodulation on Step2 priming effects. (A) Differential neuromodulation of the gain g of NMDARs conductances of glutamatergic (continuous line) and gabaergic (dashed line) neurons as a function of D1R activation by dopamine (see Eq. (3)). (B) Neuromodulation of the magnitude of Step2 priming effects by D1R activation for $b' = 0.7$. Relative magnitudes of Step2 priming (blue triangles), as difference between response times in the unrelated (gray circles) and related (blue squares) conditions, calculated as ratios of priming in each condition of D1R activation over priming for $D_1 = 1$. Step2 priming magnitude follows a bell curve, being maximal for $D_1 = 1$ and diminishing with both decreasing D1R activation for $D_1 \leq 1$ ($p < 0.05$) and increasing D1R activation for $D_1 \geq 1$ ($p < 0.05$), due to variations in response times on related (blue squares) but not on unrelated (gray circles) targets. (C1–3) Representative trials showing populations spike rates as a function of time for $D_1 = 1$, 1.5 and 2, respectively, according to the protocol D (see Fig. 1B). Priming effects are indicated by the difference between blue (related) and gray (unrelated) spotted vertical lines that indicate trial averaged time from target onset for targets population activity to reach over-threshold activity $\nu^\theta = 30$ Hz. Horizontal blue bars indicate trial averaged magnitude of Step2 priming effects modulated by *D1R* activation ($D_1 = 1$, 1.5 and 2) due to modification of reaction times in the related condition ($T_R^\theta = 136$ ms, 155 ms and 170 ms; $p < 0.5$) but not in the unrelated condition ($T_U^\theta = 204$ ms, 208 ms and 190 ms; *ns*) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

Results presented in Figs. 2B and 3C are in accordance with priming effects reported in the literature in humans (see Neely, 1991), with the increase (decrease) in prospective activity of targets neurons when preceded by a related (unrelated) prime in neurophysiological studies in monkeys (Fuster & Alexander, 1971; Miyashita, 1988; Miyashita & Chang, 1988) and with results of computational models of priming (Brunel, 1996; Brunel & Lavigne, in press; Deco & Rolls, 2005; Lavigne, 2004; Lavigne & Denis, 2001; Lavigne & Denis, 2002; Mongillo et al., 2003). The present results show that all of step1 (Fig. 2) and step2 (Fig. 3) targets are activated following a related prime. The model exhibits larger priming magnitude on step1 associates than on step2 associates, according to the experimental literature in human (Arnott et al., 2003; Hill et al., 2002; Kiefer et al., 2005; McNamara, 1992; Moritz et al., 2002; Rossell et al., 2000) and to results of the mean field model (Brunel & Lavigne, in press). The greater priming of step1 than step2 targets depends on the necessity for step1 target to be activated in order to in turn activate step2 target. Besides, when step2 target becomes activated, the feedback inhibition becomes stronger because both the prime and step1 target are already activated.

The network of integrate and fire neurons proposed here permits to differentiate time constants of the different membrane receptors AMPARs, NMDARs and GABARs, allowing to differentially neuromodulate the gain of NMDARs currents in glutamatergic and gabaergic neurons by D1R activation. We first studied if neuromodulation could replicate hemispheric difference in step1 priming, with the left hemisphere exhibiting focused priming of mainly strong associates, and the right hemisphere exhibiting extended priming of strong and weak associates (Fig. 2). If so prospective activity leading to priming effects should vary with the level D_1 of D1R activation. Data from Brunel and Lavigne (in press) show that prospective activity of neurons encoding a target depend on retrospective activity of neurons encoding the prime. In addition, data from Brunel and Wang (2001) show the largest increase in retrospective activity for decreasing D_1 between values of 1 and 1.5. To focus models simulations on the range of variation of D_1 were neuromodulatory effects on priming were the most expected, test trials were first made to compare the magnitudes of priming for values of D_1 of 1 and 1.5 (Fig. 2A). Statistical analyses of variance show that step1 priming is significant on both strong and weak associates (both $p < 0.01$), and is stronger on strong than on weak associates ($p < 0.05$). D1R activation modulates the magnitude of priming of weak associates ($p < 0.01$) but not of strong associates (*ns*). Priming modulation depends on variations in reaction times in the related condition but not in the unrelated condition (Fig. 2A). To test if the level of activation of related targets was increased in priming, and not the level of inhibition of unrelated target decreased, prospective activities of strong and weak step1 associates were calculated as trial average spike rates of corresponding neurons populations during delay (ISI) (Fig. 2B1–2). Rate of prospective activity is higher for strong than weak step1 associate ($p < 0.001$), and D1R activation modulates the level of prospective activity of weak step1 associates ($p < 0.05$) but not of strong step1 associates (*ns*).

Second, we studied if differential gain modulation (Fig. 3A) could account for greater step2 priming in the right than in the left hemisphere (Fig. 3B). Simulations data show a main priming effect of step2 associates ($p < 0.001$) and of modulation ($p < 0.01$). We first explored the modulation of step2 priming within the same range of variation of D1R activation as for step1 priming (between 1 and 1.5). Results show that the magnitude of step2 priming increases with decreasing D_1 (Fig. 3B and 3C1–2; $p < 0.05$). Then, dopamine appears to modulates the magnitude of step2 priming and step1 priming of weak associates, but not of step1 priming of strong associates. Taken together, modulatory effects of dopamine depend on both association strength and step, with variable levels of D_1 subtending priming of direct and strong associates in both hemispheres and priming of indirect or weak associates mainly in the right hemisphere. A less DA irrigated right hemisphere ($D_1 \approx 1$) would subtend extended priming of weak and strong step1 associates as well as of step2 associates. A prime presented in the LVF-RH would then spread its activation to all of its close and remote associates. A more DA irrigated left hemisphere ($D_1 \approx 1.5$) would subtend focused priming of strong step1 associates rather than of weak step1 and step2 associates. A prime presented in the RVF-LH would then activate only its close and strong associates. This supports the hypothesis that differential neuromodulation of the left and right hemispheres can lead to different semantic coding, focused or extended, respectively.

We then investigated to what extend dopamine neuromodulation is a possible mechanism underlying priming differences between healthy subjects and schizophrenic patients. At the short SOAs at which priming effects are investigated in the present research, several data report increased magnitudes of priming (hyper-priming effects) involving step1 (refs) and step2 relations, especially in patients exhibiting thought disorders (Chenery, Copland, McGrath, & Savage, 2004; Manschreck et al., 1988; Moritz et al., 2002; Spitzer et al., 1993a,b; see Minzenberg et al., 2002). The models behavior exhibits an increase of step1 priming of weak associates and of step2 priming when D_1 decreases (from 1.5 to 1), supporting the hypothesis that weaker *D1R* activation can subtend hyper-priming in schizophrenia. Step2 relations exhibit the most reliable hyper-priming effects in thought disordered patients (see Kischka et al., 1996). The possibility that low levels of *D1R* activation in schizophrenic patients could subtend hyper-priming is supported by data reporting hypo-priming in healthy subjects with L-dopa or D1R agonists (Copland et al., 2003; Kischka et al., 1996; Roesch-Ely et al., 2006). These two mirror effects are accounted for by the model within the range of variation of D_1 between 1 and 2. However, when exploring the range of neuromodulation of step2 priming, models results show that the increasing magnitude of step2 priming for decreasing values of D_1 extends to values between 1 and 2 (Fig. 3B and 3C2–3). This means that from a given value within this range (e.g., $D_1 = 1.5$), a decrease leads to hyper-priming and an increase leads to hypo-priming. When scanning the whole range of D_1 between 0 and 2, the models behavior exhibits that the modulation of the magnitude of step2 priming follows a bell-curve ($p < 0.05$) as is the case for retrospective activity (Brunel & Wang, 2001). Step2 priming is reduced for too small D1R activation where NMDA receptor mediated excitation is too weak, and for too large D1R activation where gain modulation saturates on pyramidal cells receptors but not yet on interneurons receptors, the net effect being an enhanced inhibition. Thus, there is an optimal range of D1R activation leading to bell-shaped curve for the dependence of step2 priming on D1R modulation. This suggests that hypo-dopaminergic states can lead to hyper- or hypo-priming as a function of the precise level of D1R activation considered. With regard to the facilitatory or inhibitory component of priming (see Neely, 1991) that is modulated, the reported variations in the magnitude of step2 priming are due to variations in response times on related target ($p < 0.001$) and not to variations in response times on unrelated target (*ns*) (see Lecardeur et al., 2007 for a discussion). Response times also depend on the threshold ν^θ at which spike rates trigger a response. In the range of D_1 between 1 and 2 were step2 priming effects vary monotonously, response times calculated for ν^θ, $\nu^\theta - 10\%$ and $\nu^\theta + 10\%$ increase (decrease) when threshold increases (decreases; $p < 0.05$). However neither the magnitude of step2 effects nor the effects of D1R activation on step2 priming depend on threshold (both effects *ns*). Effects of D1R activation on the magnitude of priming effects are actually caused by the modulation of prospective activity of step2 associates, calculated as trial average spike rates of corresponding neurons populations during the delay (Fig. 3C1–3). For example, when D_1 decreases from 2 to 1, prospective activity of step2 associates increases ($p < 0.05$) and activity of unrelated items is not modified (*ns*).

4. Discussion

The present research shows that biologically realistic cortical network models allow linking the mechanisms of dopamine neuromodulation at the cellular level with the variability of the magnitude semantic priming effects at the network level. Priming effects are due to activation of the target-specific neurons by prime-specific neurons after presentation of the prime, similar to the observed prospective activity in monkey experiments. They depend on the level of prospective activity of neuronal populations, determining the response time at which its activity reaches a given threshold. Priming magnitude is accounted for by neurobiological parameters such as neuronal or synaptic time constants or strength of synaptic connections encoding the semantic relationships between the items. The model of integrate and fire neurons replicates the sharp transitions of the level of activation and the variable transition times, due to the stochastic behavior of large and noisy neural structures (see Mongillo et al., 2003). The prospective activity of targets neurons is supported by neurophysiological data in monkeys (e.g., Miyashita, 1988; Sakai & Miyashita, 1991). Studies in monkeys report prospective activity leading to simple associative priming effects in the temporal areas (mostly anterior–inferior; Takeda, Naya, Fujimichi, Takeuchi, & Miyashita, 2005; Naya et al., 2001, 2003a,b; Yoshida et al., 2003; Erickson & Desimone, 1999; Sakai & Miyashita, 1991) which are involved in associative memory (see Buckley & Gaffan, 1998a; Buckley & Gaffan, 1998b; Murray, Gaffan, & Mishkin, 1993). In addition, fMRI studies in human report that both frontal and temporal areas contribute to priming, with greater effects for step1 than for step2 associates (Tivarus, Ibinson, Hillier, Schmalbrock, & Beversdorf, 2006). Hemodynamic responses revealed step1 priming primarily within the inferior prefrontal cortices and step2 priming primarily within the temporal cortices, with enhanced responses predicting thought disorder in schizophrenic patients (Kuperberg, Deckersbach, Holt, Goff, & West, 2007). Altogether, These studies suggest that the neuronal substrate for the neuromodulation of priming in human would spread over IT and PF networks in dynamic interactions.

The cortical network model presented here exhibits simultaneous activation of several neurons populations in stable attractor states in working memory (Amit et al., 2003; Brunel, 1996; Haarmann & Usher, 2001; Lavigne, 2004). A working memory capacity of several items (Haarmann & Usher, 2001; Luck & Vogel, 1997) allows prospective activity of several step1 and step2 neurons populations associated to a prime. The precise level of prospective activity depends on the ratio of activation/inhibition received by activated neuronal population (Brunel, 1996; Amit & Brunel, 1997). In the model network, prospective activity of step1 associates arises rapidly in a few tens of milliseconds (Beauvillain & Segui, 1983;

Fischler, 1977; Fischler & Goodman, 1978; Lee et al., 1999; Lukatela & Turvey, 1994; Perea & Gotor, 1997; Perea & Rosa, 2002; Rastle, Davis, Marslen-Wilson, & Tyler, 2000; Sereno, 1991).

4.1. Neuromodulatory effects on hemispheric semantic coding

The model of integrate and fire neurons shows that discrimination between priming of strong and weak associates can vary with the level of differential dopaminergic neuromodulation of NMDARs of glutamatergic and gabaergic neurons. Within this framework, processing of a prime generates different levels of associated targets 'signals' above background noise depending on neuromodulation. Within the range of D1R activation between 1 and 2, high levels of D1R activation induce focused activation of strong and step1 associates. This corresponds to focused priming of small semantic fields such as reported mainly in the RVF-LH. Low levels of D1R activation induce extended activation of step2 and weak step1 associates. This corresponds to extended priming of large semantic fields such as reported mainly in the LVF-RH (Beeman et al., 1994, 2000; Beeman & Chiarello, 1998; Chiarello et al., 2003; Jung-Beeman, 2005). Differences in DA neuromodulation can set the network in a focused or extended mode of semantic processing. These results can also account for stronger step2 priming in the LVF-RH than in the RVF-LH (Richards & Chiarello, 1995; Yochim et al., 2005). Both hemispheres would then contribute to semantic processing in different ways; the LH would be more involved in processing of dominant and context-specific information (Hutchinson et al., 2003), while the RH would be more involved in integrating large discourse representations (e.g., Kaplan, Brownell, Jacobs, & Gardner, 1990) such as metaphors (Brownell, Simpson, Bihrle, Potter, & Gardner, 1990; Winner & Gardner, 1977).

4.2. Schizophrenia

Simulation data on step2 priming are in agreement with experimental data reporting that activation of D1R at the cortical level can diminish the magnitude of step2 priming on healthy subjects (Copland et al., 2003; Kischka et al., 1996) especially in the left hemisphere (Roesch-Ely et al., 2006). Model results support the hypothesis that an increase in cortical dopamine, such as under stress (see Kischka et al., 1996), would lead to focused priming of step1 associates but not of step2 associates. Interestingly, the symmetric behavior of increased step2 priming when D1R activation decreases is in accordance with experimental data reporting hyper-priming in schizophrenic patients (Arnott et al., 2003; Chenery et al., 2004; Manschreck et al., 1988; McDonald, Brown, & Gorell, 1996; Moritz et al., 2002; Spitzer et al., 1993a; Spitzer et al., 1993b; see Minzenberg et al., 2002). In addition, simulations show that the pattern of hyper- or hypo-priming reported in schizophrenic patients is sensitive to the precise level of D1R activation. For decreasing neuromodulation from highest to medium values, step2 targets exhibit hyper-priming. When D1R activation further decreases to the lowest values, the model exhibits hypo-priming such as reported in some studies (see Barch et al., 1996; Besche et al., 1997; Gouzoulis-Mayfrank et al., 2003).

4.3. Neuromodulatory and synaptic hypothesis of priming variability

Model results support the hypothesis that differential neuromodulation between the two hemispheres, as well as between healthy and shizophrenic subjects, can exhibit different priming effects as a function of step, synaptic strength and level of D1R activation. The model results show that the precise level of D1R activation is a critical parameter determining the pattern of hyper- or hypo-priming obtained, due the bell-shaped curve describing the dependence of priming effects on D1R activation. The present research shows that neuromodulation of a cortical network of integrate and fire neurons at the receptor level can lead to differential variability of step1 and step2 priming such as reported in the literature. This suggests a link between hemispheric differences and priming dysfunctions in schizophrenia based on a common mechanism of normal or abnormal dopamine neuromodulation A parallel research used the mean field approach to test for the effects of differential synaptic potentiation on the magnitude of priming (Brunel & Lavigne, in press). It showed that differential levels of synaptic transmission can account for inter hemispheric differences in priming as well as for some perturbations in schizophrenia, in accordance with the synaptic hypothesis of different microcircuitries of the left and right cortical areas (Beeman & Chiarello, 1998; Hutsler & Galuske, 2003; Jung-Beeman, 2005; see Galuske, Schlote, Bratzke, & Singer, 2000). In addition, differences in synaptic transmission could rely on structural differences of association fibers at the cellular level and/or on aberrant control of synaptic plasticity in schizophrenic patients through NMDAR hypofunction (Hoffman & McGlashan, 1993; Javitt & Zukin, 1991; Phillips & Silverstein, 2003) or abnormal dopaminergic modulation of NMDAR (Stephan, Baldeweg, & Friston, 2006) and/or abnormal (Braver, Barch, & Cohen, 1999; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992). Then the issue could be not to pick out one or the other hypothesis, i.e., neuromodulatory or synaptic, but to understand their synergetic actions on priming. In cortical networks NMDAR hypofunction and neuromodulation bias neurons retrospective activity (Brunel & Wang, 2001) which determine synaptic learning between neurons populations (Amit & Mongillo, 2003; Mongillo et al., 2003; Brunel, 1996). The present study shows in turn that synaptic efficacy determines the sensibility of retrospective and prospective activities to neuromodulation to modify the magnitude of semantic priming effects. Though accounting for a large part of the results in the literature, the present study focused on the dopaminergic hypothesis and does not bring strictly identical results to the one focused on the synaptic hypothesis (Brunel & Lavigne, in press). Synaptic effects tested by the authors predict enhanced contrast between priming of strong vs. weak step1 associates in the left compared to the right hemisphere. This occurred through combined increase of priming of strong associates and decrease of priming of weak associates. Neuromodulatory effects tested with the model of integrate and fire neurons predict enhanced contrast for higher values of D1R activation through a decrease of priming of weak associates without increased priming of strong associates. These predictions suggest that further experimental studies, comparing step1 priming of strong and weak associates in the two hemispheres or in schizophrenic patients, could give good insights on the type of neuromodulatory or synaptic effect primarily involved. Predictions of the models may also help conducting experiments testing for the neuromodulatory or synaptic effects by testing experimentally step2 priming as a function of association strength, in divided visual field experiments. This points to the importance of precisely measuring and controlling the type of relation and association strength involved in prime-target pairs used as experimental material.

5. Conclusion

In this research we have focused on the most consensual data in the literature regarding the possible relations between dopamine and magnitude of semantic priming. However, conflicting results are somewhat reported on the possibility for either hypo- or hyper-priming in schizophrenia. Further modeling approaches may be

fruitful in systematically exploring larger ranges of variations of those parameters, adding the prime-target delay, and define more precise predictions. The present results of the model show that the type of relation involved, association strength and level of D1R activation, co-influence priming magnitude. This points to the importance of estimating the level of D1R activation in participants to experiments, and test priming effects in healthy vs. schizophrenic patients under controlled dosages of DA vs. NMDA agonists/antagonists. More anatomical and neurochemical data is clearly needed, to better understand the synaptic and neuromodulatory hypothesis on semantic priming. The reciprocal enrichment of the experimental and modelling approaches is twofold: computational modelling is a way to give a unified account of various types of data and test for the effect of neurophysiological factors influencing priming that are difficult to measure and quantify; and behavioral and neurophysiological data enable elaborating more realistic models of cortical networks to bridge the gap between the cellular and behavioral levels.

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