Review article

Why context matters? Divisive normalization and canonical microcircuits in psychiatric disorders

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ABSTRACT

Neural activity on cellular, regional, and behavioral levels shows context-dependence. Here we suggest the processing of input-output relationships in terms divisive normalization (DN), including (i) summing/averaging inputs and (ii) normalizing output against input stages, as a computational mechanism to underlie context-dependence. Input summation and output normalization are mediated by input-output relationships in canonical microcircuits (CM). DN/CM are altered in psychiatric disorders like schizophrenia or depression whose various symptoms can be characterized by abnormal context-dependence.

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Psychiatric disorders such as schizophrenia and depression are typified by symptoms where subjects seem to be detached from their respective environmental, social and behavioral contexts. For instance, auditory hallucinations in schizophrenia signify internal voices that occur spontaneously and are not related to any person actually speaking in the respective social context (Ford et al., 2014; Northoff 2015a, 2015d). Analogously, ruminating thoughts in depressed patients about, for instance, guilt, financial worries, or self-blame remain independent of reality, i.e., of their environmental, behavioral or social context (Northoff, 2007; Northoff and Sibille, 2014). Thus, a complex and not yet well-understood disruption in the interaction between the brain's neural activity and its respective environmental, social, and behavioral context is suggested to be at the root of mental disorders.

What is meant by the term context here? Taken in a very basic sense in reference to input stimulus processing, context refers to all inputs other than the input of interest. One particular input –

such as an auditory input – is, for instance, processed in relation to and in dependence of other accompanying or co-occurring inputs (like visual and olfactory inputs). Context-dependent processing can also be observed on the side of the output. The output is not only processed in relation to one particular input it is supposed to result from, the input of interest, but is also dependent on other inputs and hence on the totality of inputs (See below for a more detailed definition of context). Accordingly, the notion of context as defined here refers to the most basic processing of inputs and outputs on cellular and regional levels, with each shaping the context for the other.

This basic notion of context-dependence in terms of input and output processing may ultimately lie at the very basis of its more complex determinations as in sensory, i.e., cross-modal sensory processing where one cross-modal sensory stimulus (like an auditory stimulus) forms the context for another one (like a visual stimulus) (van Atteveldt et al., 2014v). Analogously, such basic notion of context may also underlie its cognitive determination where specific contents shape the context for voluntary psychological functions, such as value assignment in reward and decision-making (Maren et al., 2013). Rather than focusing on the higher, i.e., sensory and cognitive levels of context-dependence, we restrict ourselves to the most basic operational level in terms of input and output processing. More generally, we assume that our basic notion of context in terms of input-output processing may ultimately underlie the dependence of perception, motor behavior, and decision-making on their respective behavioral, vegetative, cognitive, social, and cultural contexts (van Atteveldt et al., 2014v; Ohshiro et al., 2011) (see below for details).

However, the neural mechanisms of context-mediated effects remain unclear. What are the underlying canonical integrative computational mechanisms? One such mechanism may be divisive normalization. According to divisive normalization, single neuron firing rates or the activity level of a population of neurons (or of a whole region or network) depend upon the ratio of the individual neuron's (or neuronal population's) response to the summed activity of a pool of other neurons or regions, respectively (van Atteveldt et al., 2014v; Carandini et al., 2012; Louie et al., 2014) (rather than on the single stimulus itself). Divisive normalization has been observed at both the cellular and regional levels in different parts of the brain, including the visual cortex, auditory cortex, and prefrontal cortex (Ohshiro et al., 2011; Louie et al., 2014).

The first aim of our paper is to show that divisive normalization can account for basic context-dependence in terms of input-output processing as defined above. This in turn, we suggest, provides the basis for the observed context-dependence on different levels of neural activity, ranging from the cellular to the population and regional/network levels. The second aim of our paper is to demonstrate how divisive normalization emerges as a natural consequence of the input-output relationships in canonical microcircuits and, particularly, their different types of GABA-ergic interneurons (somatostatin and parvalbumin expressing – see below). Focusing on GABA-ergic inhibitory interneurons, it shall be mentioned that we leave out and thus do not consider other types of interneurons like excitatory interneurons (for the sake of simplicity) which thus will need to be included in future accounts. This addresses the question of how the brain can pool, sum and normalize the activity of a single neuron/population/region in relation to others to account for context-dependence. The third aim is to demonstrate how canonical microcircuits, including their different interneurons and input-outputs relationships, are altered in psychiatric disorders, such as schizophrenia and depression, leading to abnormal context-dependence as manifest in psychiatric symptoms.

1. Context-dependence

We defined context in a basic sense in terms of input-output processing. Context-dependence in input-output processing is carried over to other higher levels of neural activity including cellular, population, and regional levels. Neurons whose firing can be related to different stimuli depending on the context have therefore been described as 'mixed neurons' showing 'mixed selectivity' (Mante et al., 2013; Woolley et al., 2014). For instance, neurons in monkey dorsal prefrontal cortex change their selectivity to color cues when the behavioral context requires selection of action based on color. In contrast, the same neurons change their selectivity to motion cues in a behavioral context that favors selecting action based on motion (Mante et al., 2013; Woolley et al., 2014). Analogous neurons showing 'mixed selectivity' have been observed in the control of movement. Neurons in monkey posterior medial prefrontal cortex do not encode a particular movement, e.g., reaching out, but rather the overall tactic, e.g., reaching toward or away from a salient target, that provides the behavioral context for a movement (Matsuzaka et al., 2013; Stokes et al., 2013).

Functional MRI (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) have revealed that analogous context-dependence (or 'framing') can be also observed at the regional level. For example, reward-related activity in the ventral striatum during a gambling task changes depending on the social context. Where a participant always receives the same magnitude of reward (such as $30), the activity level in the striatum is high only in the case where other (fictive) people are known to receive a lower sum (say $10). In contrast, the activity level is reduced when the participant is informed that the other people receive a higher sum than they do (like 60$) (see (Mante et al., 2013) as well as (Miller and Fusi, 2013; Sakamoto et al., 2013)).

Similarly, vegetative (Paulus, 2007), and cultural (Han and Northoff, 2008; Han et al., 2013) contexts strongly modulate neural activity during the presentation and processing of specific stimuli or tasks (see REF. (Han et al., 2013) for a recent review). For instance, an exteroceptive stimulus with a conditioned association with cold water may be rewarding (and induce ventral striatum activity) only if the organism itself and its interoceptive milieu show a high internal temperature such that thirst is generated (Montague and King-Casas, 2007); see also (Northoff, 2014a) chapter 8). If, in contrast, the organism and its interoceptive milieu have instead a low internal temperature, where no thirst is generated, the same exteroceptive stimulus is no longer rewarding and will not induce any activity in the striatum ((Montague and King-Casas, 2007); see also (Paulus, 2007)). Thus the body's interoceptive milieu frames and contextualizes exteroceptive stimulus processing and its related neural activities entailing what can be described as "vegetative context-dependence" (Northoff, 2014a).

Taken together, context-dependence seems to be a basic feature of the brain's neural processing that holds across different levels (cellular, population and regional), domains (perception, reward, action, decision-making and others) and contexts (vegetative, social, behavioral, and cultural). We now assume that such context-dependence on different levels and domains of neural activity may ultimately be traced to its most basic notion in terms of input-output processing as defined above, for which the computational mechanisms of divisive normalization may be crucial.

Context-dependence - Divisive Normalization How can we understand context-dependence at the levels of cellular and regional activity? We postulate that divisive normalization may serve as the computational mechanism underlying context-dependence at both cellular and regional levels of neural activity.
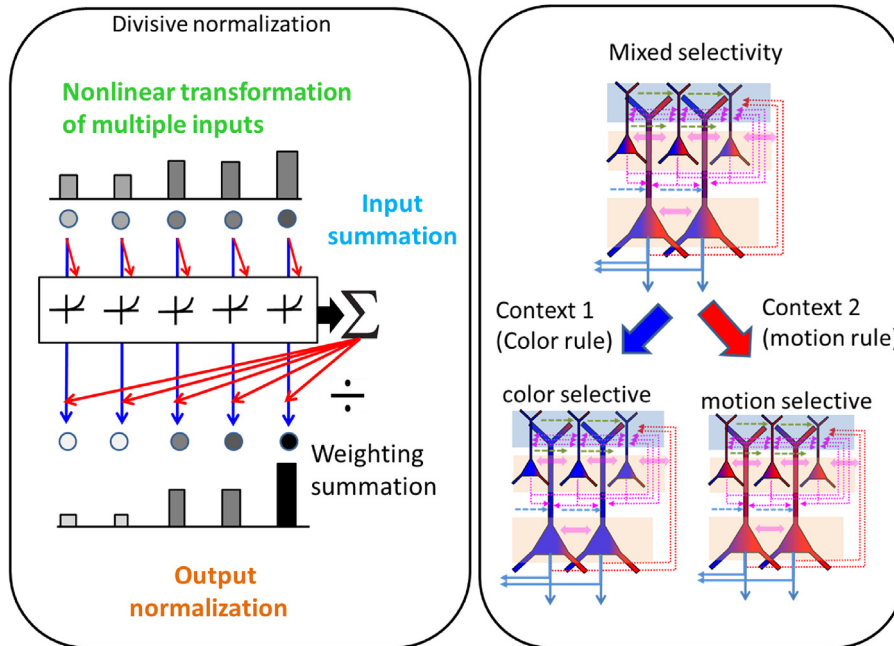
Normalization and context-dependence

Fig. 1. Divisive normalization and context-dependence.
Left Top: Divisive normalization includes two-stage operations: *input summation* and *output normalization*. Normalization is characterized by gain functions or both input and output, i.e., input/output gain functions. **Right:** the neurons with mixed selectivity to color and motions can operate under two behavioral rules; e.g.; color-rule and motion-rule (Mante et al., 2013). In the context of colour, these neurons show color selectivity whereas in a motion context, the same neurons show motion selectivity. According to divisive normalization, the behavioral context, e.g., colour or motion, shifts weighting between color and motion in output summation or output gain such that normalized outputs preferentially encode one of two behavioral parameters (see also (Ariely and Wallsten, 1995).

Divisive normalization is a canonical operation to explain how integrative outputs are produced by surrounding inputs (Carandini et al., 2012; Louie et al., 2013) One study (Louie et al., 2013) demonstrated that a divisive normalization model based on monkey and human data can be used to predict actual decision-making under reward-related conditions: the authors constructed dynamic divisive normalization models consisting of paired excitatory and inhibitory units for each specified choice alternative. Inhibitory units summed all inputs and feedback to pyramidal neurons by dividing current inputs and background activity. Such models predict the process of decision-making based on input values and furthermore incorporate a time-weighted average of past activity (as an intrinsic reference-dependence in value coding) (see Box 1 for questions revolving around coding) (Louie et al., 2013) (see also REF. (Louie et al., 2014)) (see below for details). These and other results, such as in cross-modal integration, (van Atteveldt et al., 2014v; Ohshiro et al., 2011) strongly suggest that divisive normalization describes a fundamental integrative mechanism that operates across cellular, population, regional levels, across perception, cross-modal, decision-making and reward domains.

Divisive normalization is a gain function (see also (Mejias et al., 2014; (Sutherland et al., 2009)) and can be defined as:

$$Output_i = \frac{W * input_i^N}{H^N + \sum W_i^* input_i^N}$$

This equation describes mapping of an input vector to an output vector (Fig. 1). $Output_i$ is an output value that is normalized from an input value, $input_i$. W signifies an output gain, and H is overall responsiveness that is related to the gain function and its reference point, reflecting the long-term history of inputs (see Box 1 for characterizing H in terms of the brain's spontaneous or intrinsic activity). N is the exponent that determines the slope of the gain function. The denominator of this hyperbolic function gives rise to

the pooled response by weighted summation of all input drives in relation to reference point H. H and W are subject to change depending on prior input experience (including past and present other inputs) or the expected context (as predicted outputs based on predictive coding, see Box 1) and domain values. The numerator $Input_i$ is normalized by summation of the populations and H, such that the response level is adjusted and mapped to the normalized response curve. In this way, the respective system operates across a wide range of intensities and maximizes sensitivity across different environments; that is, contexts (vegetative, cultural, social, behavioural and cognitive)

How does divisive normalization allow for the processing of inputs and outputs? Suppose there are various neurons with different combinations of selectivity for two stimuli's attributes (such as color or motion). According to divisive normalization, all inputs are summed along the two feature values, with the different inputs (like color and motion) being encoded (i.e., summed) relative to each other, amounting to what we describe as 'input summation'. Divisive normalization extends even further though, namely to the output. The output is generated (i.e., normalized) relative to the input (and various normalization parameters as above) resulting in what we describe as 'output normalization'. Even if the actual input remains the same, the output may nevertheless change and thus be normalized in a different way depending on W, the output gain, and the H, the overall responsiveness (that includes the input history of, for instance, that particular input). Accordingly, output normalization allows adapting the output to its respective context, as instantiated in the actual input, the past inputs (i.e., H), and the output gain (i.e., W). Take the above described example of the neurons' mixed selectivity for either color or motion. If the gain or weighing functions are higher in color than motion, color selectivity is maintained while motion selectivity is decreased. In contrast, if the gain or weighing function is higher in motion than color, motion selec-

tivity will be maintained while color selectivity will be decreased. Due to asymmetric processing in divisive normalization, the original symmetric distribution is compressed for one attribute and stretched for the other according to the nonlinearity of hyperbolic functions. In this way, the final output shows increased selectivity for one feature and, at the same time, decreased selectivity for the respective other feature.

2. Canonical microcircuits – "Input summation" and "Output normalization"

How is divisive normalization and its two stages of input summation and output normalization implemented in the nervous system? The answer to this question leads us to the canonical microcircuit, which is the most basic functional unit of input–output processing (Markram et al., 2004).

Canonical microcircuits are characterized by pyramidal excitatory neurons and different inhibitory interneurons that target the dendrites and axons of pyramidal excitatory neurons (Markram et al., 2004) (while we here, for the sake of simplicity, other types of interneurons like excitatory interneurons). GABAergic interneurons can be classified into parvalbumin-expressing fast-spiking interneurons (PV), including basket and chandelier cells, and somatostatin-expressing interneurons (SST), including Martinotti cells (see Roux and Buzsáki, 2015) for review). The remaining subsets of GABAergic interneurons include a neuroglial form and bipolar and vasointestinal peptide-expressing multipolar interneurons (Markram et al., 2004; Ascoli et al., 2008; Kepecs and Fishell, 2014). Although fewer than 20% of neurons in the cortex are inhibitory, they nevertheless have a central role in controlling how pyramidal cells function in neural operations (Roux and Buzsáki, 2015) (Fig. 2).

More specifically, PV neurons are located in layers 3 and 4 (which is the major thalamo-cortical projection recipient layer) and terminate on the bodies of pyramidal cells and on the proximal parts of their axons and dendrites (Danziger et al., 2011; Gentet, 2012). Due to their proximal termination, inhibitory PV neurons induce feed-forward suppression of dendritic input to pyramidal cells and feedback suppression to axonal output. Activation of PV-expressing neurons enables pyramidal cells to receive inputs thorough dendrites by dis-inhibiting SST neuronal dendrites (Roux and Buzsáki, 2015; Danziger et al., 2011; Gentet, 2012).

By contrast, inhibitory SST neurons are mainly located in upper layers 1 and 2 of the cortex, where they predominantly exert inhibitory input to the long-ranging dendrites of the pyramidal cells that convey inputs from cortico-cortical connections within the same and across different regions (Sibille and French, 2013). Thus, the activation of SST interneurons inhibits dendritic inputs and isolates the proximal portions of the pyramidal cells to protect them from remote inputs, particularly those from cortico-cortical connections. Due to their location in layers 1 and 2, SST interneurons control cortico-cortical inputs, conveying a strong spatial dimension (from either different regions or different cells) in input processing; thus, they modulate the processing of particular inputs to other cortical microcircuits, neuronal populations, and regions. Although they are not directly affected by the inputs themselves, the connected populations and regions modulate input summation by sending cortico-cortical connections that terminate in layers 1 and 2. Since the different inputs originate in different cells or regions, their summing links together spatially segregated inputs into one input in one particular cell, population, or region, amounting to what we describe as 'spatial input summation'. Due to its integration of inputs from different cells and populations, such spatial input summation allows for the extension of divisive nor-

malization from cellular to population (and even regional and network) levels of neural activity (see Fig. 2).

The control of pyramidal cells by the different types of interneurons implies that both inhibitory and excitatory inputs can be set and compared with each other; that is, normalized against the ongoing spontaneous activity levels of pyramidal cells (Northoff, 2014a; Hansen and Neumann, 2008; Nassi et al., 2014). Importantly, the different relationships of SST and PV interneurons with pyramidal cells including their modulation of excitation suggest that both interneuron populations exert different roles in divisive normalization.

PV neurons equalize excitation–inhibition ratios and dynamically adjust excitation and inhibition of innervated pyramidal cells (Xue et al., 2014), whereas SST neurons control the input gain of dendritic synapses (Kepecs and Fishell, 2014). Importantly, one and the same SST neuron can control different dendrites (Roux and Buzsáki, 2015) and hence inputs from different cells, populations, and regions/networks. That makes SST neurons an ideal candidate for averaging target and background, as the first step in divisive normalization.
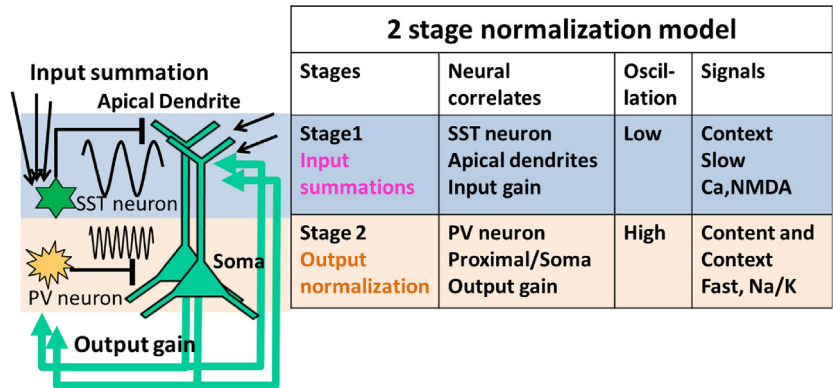
By contrast, PV neurons are perfectly suited for the second divisive normalization stage as they directly control the soma of the pyramidal cells and thus their output. Such output control alone is, however, not sufficient in itself for normalizing the output against the input; for that a direct link between input and output processing and thus between SST and PV neurons is required. This is indeed the case since SST neurons (as related to the input processing) suppress PV neurons (as related to output processing) and thereby indirectly dis-inhibit pyramidal cells (Cottam et al., 2013). This interaction between SST-PV-neurons (e.g., between input and output processing) seems to operate in a non-linear way (Roux and Buzsáki, 2015) (e.g., one SST neuron disinhibits several pyramidal cells through their suppression of PV-neurons) which may be central for normalizing the output against the input, i.e., output normalization.

The assumption of the different roles of SST and PV neurons in divisive normalization is further supported by observations stemming from the sensory cortices. PV interneurons in the visual cortex alter response gain in a divisive manner, whereas SST interneurons shift response levels in a subtractive manner (Wilson et al., 2012). Other studies have demonstrated that SST neurons mediate suppression via feedback inhibition driven by intrinsic lateral connections (Adesnik et al., 2012). In contrast, PV neurons mediate global gain via feed-forward inhibition (Nienborg et al., 2013). These specific effects of SST and PV are compatible with the occurrence of non-linearity and widespread lateral inhibition as characteristic features of divisive normalization in visual and other sensory cortices (Carandini et al. 2012; Adesnik et al., 2012; Kapfer et al., 2007) Future accounts and studies may also include other excitatory interneurons in their models and investigation for further refinement and specification.

3. Canonical microcircuits - slower and faster oscillations

Finally, different inhibitory neurons provide temporal windows of opportunity for selectively exciting pyramidal cells to integrate ensembles of different inputs and normalize output against input using oscillatory mechanisms (Roux and Buzsáki, 2015; Buzsáki and Wang, 2012). Inhibitory cells receive convergent inputs from pyramidal cells and tend to oscillate at distinct frequencies. PV interneurons (and their location within layers 3 and 4) are central for inducing higher frequency oscillation ranges, including gamma, in local canonical microcircuits, (Rou and Buzsáki, 2015; Buzsáki and Wang, 2012; Womelsdorf et al., 2014). By contrast, SST interneurons (and their location within layers 1 and 2) have

Two stages of normalization

2 stage normalization model			
Stages	**Neural correlates**	**Oscil-lation**	**Signals**
Stage1 Input summations	**SST neuron** **Apical dendrites** **Input gain**	**Low**	**Context** **Slow** **Ca,NMDA**
Stage 2 Output normalization	**PV neuron** **Proximal/Soma** **Output gain**	**High**	**Content and** **Context** **Fast, Na/K**

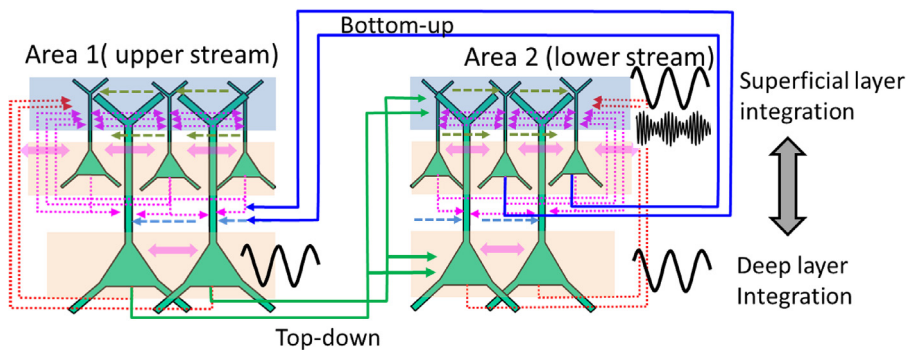## Across-laminar and Inter-regional interaction

Fig. 2. The two stages of divisive normalization and the across-laminar and inter-regional microcircuits.
Top The two stages of divisive normalization, input summation and output normalization, are closely related to different interneurons, Somatostatin (SST) and Parvalbumin (PV) and their different relationships to pyramidal cells. Pyramidal cells consist of two segments: apical dendrites which contribute to inputs summations and soma which contributes to output normalization with feedforward and recurrent inputs. SST neurons are situated at the apical, e.g., distal dendrites of the pyramidal cell; there SST neurons receive surrounding inputs, calculate input summation and control input gains to apical, e.g., distal dendrites which receive excitatory inputs from various cells, populations, and regions/networks. in contrast, PV neurons are situated at the proximal dendrite and soma of the pyramidal cell; this makes it possible for the PV-neurons to contribute to output normalization by controlling output gain at proximal dendrites and soma.
In the temporal domain, SST neurons contribute to generating oscillation at slower frequency (like delta) while PV neurons contribute to the generation of higher frequency oscillations (like gamma). Thus normalization and oscillations synergistically contribute to the temporal dynamics of input-output relationships by timing both input summation and output normalization against the ongoing intrinsic oscillations.
Bottom: In across-laminar circuits, inputs are processed at superficial layer and deep layer. The superficial layer contributes to encoding prediction errors and sending them to the upper stream area (Bastos et al. 2012; Wang, 2010). The deep layer contains large pyramidal cells with dendrites and contribute to across-laminar integration thereby sending top-down signals to the lower stream area (Bastos et al. 2012; Wang, 2010). Lower and higher frequency oscillations are observed in multi-layer structure. Lower frequency oscillations (like delta and theta) are found in superficial layer in layer 2/3 and deep layers (Lakatos et al. 2008). In contrast, higher frequency oscillations (like gamma) are found near the soma in layer 2/3 and are often coupled with lower oscillations.
SST = Somatostatin, PV = Parvalbumin

a complementary role in slow, lower and mid-range oscillations, including delta, theta and beta oscillations during long-range interactions that extend from single cells over populations to regions (and even networks) (Womelsdorf et al., 2014; He and Raichle, 2009), (Northoff, 2015a, 2015d) (see Fig. 2).

Due to the association of SST and PV neurons with different frequency oscillations (Matsuzaka et al., 2012), we postulate that the two core DN stages — input summing and output normalization — may be related to oscillations at different frequencies. More specifically, we assume that summing or averaging inputs, as computed mainly by layers 1 and 2 and their SST interneurons, is related to lower frequency oscillations, particularly delta (see also van Atteveldt et al., 2014v): their rather long cycle durations makes them suitable to integrate different inputs at distinct (though closely related) time points into one high excitability period at the trough of the oscillation. This is further supported by the fact that slow oscillations, such as delta, are central to the encoding and entraining of inputs (Northoff, 2014a; Lakatos et al., 2008; Stefanics et al., 2010) (see Box 1 for discussing encoding strategies).

By contrast, we postulate that normalizing output against input may involve higher frequencies, such as gamma. Output is computed mainly in layers 3 and 4 by pyramidal cells that are under the control of PV neurons (see (Wilson et al., 2012; Lee et al., 2012; Pouille et al., 2009)) that are predisposed to fast oscillations, such as upper gamma (> 60 Hz) and high gamma (100–250 Hz) (Arnulfo et al., 2015). Output must be temporally precise, with the need for it to occur at one particular discrete time point, which makes the PV neurons an ideal candidate to account for output normalization (which also reconciles the recent discussion as to whether divisive normalization is associated with either SST or PV inhibitory interneurons in (Arnulfo et al., 2015) and (Lee et al., 2014) by assuming that both interneurons are involved in divisive normalization, albeit in different ways in its distinct stages, i.e., input summation and output).
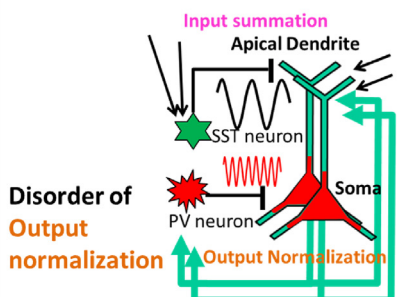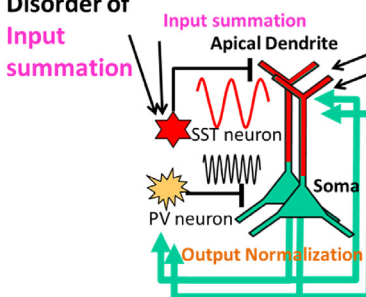
Fig. 3. Two stages of divisive normalization in mental disorders.
The figure shows the relationship between two major mental disorders of schizophrenia (left) and depression (right) and the two stages of divisive normalization.
Left: Various symptoms in schizophrenia like auditory hallucinations, delusions, and ego-disturbances are characterized by detachment or dissociation of the perceptual and cognitive contents from their respective spatiotemporal, e.g., behavioral and social context, amounting to content-context dissociation. One neural correlate of such content-context dissociation may be found in abnormal output normalization as mediated by deficits in PV neurons that control the pyramidal cell's output with high frequency oscillations like gamma which are indeed deficient in schizophrenia.
Right: Various symptoms like ruminations, feelings of guilt, delusional contents like being poor, and others in major depressive disorder are characterized by that subjects remain unable to modify these perceptual, affective, and cognitive contents according to their respective spatiotemporal, e.g., social and behavioral context, e.g., contextual inputs amounting to predominance of context over content, e.g., content-dependence. Neural correlates for such abnormal content-dependence may be found, in part, in abnormal input summation as mediated by deficient SST neurons that no longer allow for proper input summation and its association with low frequency oscillations which are indeed deficient in depression.

Specifically, output normalization is most likely to occur by aligning the output to the PV-interneuron mediated extremely short cycle durations of fast oscillations to preclude interference with other outputs (and inputs). Output normalization may consequently be characterized by a strong temporal dimension, accounting for what we describe as 'temporal output normalization'.

4. Psychiatric disorders – Abnormal "input summation" and/or "output normalization"

Psychiatric disorders can be characterized by abnormal changes at both cellular and regional-network levels of neural activity. However, how cellular and regional levels are linked and how their abnormalities transform into psychiatric symptoms remains unclear. We postulate that psychiatric disorders can be characterized by changes in both canonical microcircuits and divisive normalization. Most importantly, these changes are proposed to underlie a physiologically based computational mechanism that may allow accounting for psychiatric symptoms, including their abnormal context-dependence. It shall be noted that we here only capture abnormalities in microcircuits in these disorders while leaving open how they transform onto the regional and network level. Without going into details, we suggest that the canonical microcircuits that are pervasive throughout the whole brain are nested and contained as basic unit within the larger spatiotemporal scale of regional and network levels. Such temporo-spatial nestedness implies that the abnormalities of the canonical microcircuits, as for instance their abnormal oscillation pattern re-occur and are amplified on the regional and network level where they can be related to specific symptoms.

Here, we focus on two key disorders — schizophrenia and major depressive disorder (MDD). In a nutshell, we will characterize schizophrenia by abnormal output normalization while MDD shows altered input summation. However, as we discuss in Box 2, the data do not support exclusive specificity of these mechanisms for either MDD or schizophrenia. Instead, the mechanism involved may also vary between different regions of the brain like auditory cortex or dorsolateral prefrontal cortex. In the following, we focus mainly on the two mechanisms and their predominant association with either MDD or schizophrenia; that will be complemented by Box 2 where we discuss the involvement of the two mechanisms in different regions in the two disorders.

4.1. Schizophrenia

Schizophrenia is a multifaceted disorder that is characterized by positive delusional symptoms, auditory hallucinations, thought disorders (thought disorganization and blockade), ego- or identity disturbances, and so-called negative symptoms, such as blunted affect, social withdrawal and retarded psychomotor function. Postmortem studies have demonstrated specific PV interneuron deficits (involving chandelier and basket cell types) in layers 3–5 of the dorsolateral prefrontal cortex (DLPFC) (Arion et al., 2015; Volk et al. 2012), leading to well-known deficits in gamma oscillations and cognitive disturbances, such as working-memory deficits (see REF's (Lewis, 2014; Lewis et al., 2012; Uhlhaas and Singer, 2014) for reviews).

A deficit in PV interneurons means that both dendrites and axons proximal to the pyramidal cell body are no longer inhibited properly. Thus, the output from the pyramidal cell body is no

longer set properly versus its input; that is, normalized as described in the second DN step (see above). Therefore, schizophrenia may be characterized by divisive normalization deficits (see also REFs (Carandini et al., 2012; Lewis, 2014)), which may be specified as a deficient normalization of output.

Due to the lack of PV interneuron-based inhibition, a deficiency in gamma oscillations results (see (Lewis, 2014; Lewis et al., 2012)), making it impossible to precisely tune output temporally. Such imprecise or lack of temporal tuning of output — that is, deficient temporal output normalization — may be manifested in temporal disorganization and blocking of goal-orientation thoughts (as mediated in the DLPFC) (see (Northoff 2015a, 2015d; Northoff, 2014c) and (Northoff 2015a, 2015d) for a temporal interpretation of cognitive symptoms in schizophrenia as well as (Montague et al., 2006; Javitt, 2009), for such a spatiotemporal approach to psychopathological symptoms in general). To temporally normalize the output against the input allows for proper and temporally precise prediction of future inputs as described in predictive coding (Box 1). If, however, the output is no longer properly temporally normalized — that is, contextualized against the input — the output may no longer carry proper contextual or predictive information about future inputs. The resulting behavior becomes consequently decontextualized, i.e., dissociated from its respective spatiotemporal context, which is exactly what one can observe in schizophrenia.

Interestingly, somewhat analogous changes can be observed in the auditory cortex, where layer 3 dendritic spines and pyramidal neurons seem to be deficient in schizophrenia (Dorph-Petersen et al., 2009; Sweet et al., 2009). These changes in pyramidal neurons may reverberate upon PV interneurons (which, in response may be down-modulated to lower the degree of inhibition of the reduced number of pyramidal cells) and consequently the degree to which the output can be temporally normalized against the input. At worst, the generation of the output may be completely dissociated or decoupled from the processing of inputs, such that outputs are generated independently.

This may for instance be the case in auditory hallucinations: internally generated outputs are falsely taken for externally generated inputs, which results in the experience of hearing voices that are taken to be externally generated and located in the outer world. This, we assume, is possible only when confusing input and output (see also (Northoff, 2014c; Northoff and Qin, 2011)), which in turn presupposes deficient output normalization (against the input), with subsequent decoupling between input and output processing. Abnormal output normalization makes the proper prediction of future inputs impossible which, as we assume, should shape the regional and networks level of activity in abnormal ways. This may be manifested in abnormal predictive coding which, as it has been shown, underlies some of the typical symptoms of schizophrenia, such as hallucinations (Horga et al., 2014) and delusions (Adams et al., 2013; Teufel et al., 2010),. Interestingly, both hallucination and delusion can be characterized by spatial and temporal dissociation from the respective social and behavioral context (see Fig. 3). Together, we tentatively assume that the abnormal content-context relation is transferred from the cellular level of cortical microcircuits over the regional and network level to the level of symptoms and behavior.

4.2. Depression

How are changes in canonical microcircuits and divisive normalization involved in MDD? MDD is a multifaceted disorder that involves affective symptoms (sadness and anhedonia), cognitive changes (deficits in executive function and attention) and somatic symptoms (for example, heart palpitations and nonspecific pain). Postmortem and genetic studies show deficits in layer 1 and 2 SST interneurons in the DLPFC, whereas PV interneurons remain

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Box 1: Divisive normalization and difference-based encoding

Divisive normalization and coding

What coding strategy might divisive normalization involve? Several coding strategies have been suggested at both cellular and regional levels (see (Northoff, 2014a) for an overview) which we assume to co-occur and complement each other rather than being contradictory and mutually exclusive.

Adaptive coding: The concept of adaptive coding has been suggested as a cellular level coding strategy to account for context-dependence (Stokes et al., 2013; Duncan, 2013). Adaptive coding implies that a single cell receives a variety of inputs from other cells, with the inputs stemming from external (sensory and motor) and internal (values, memories, etc.) environments: such input summation produces the observed activity, i.e., outputs in such way that for instance cellular firing rates adapt to these inputs. Most importantly, adaptive coding states that these neurons' firing rates can encode multiple messages, depending on the respective contextual constellation of inputs; thus, mirroring output normalization (see for instance (Stokes et al., 2013) as well as (Mante et al., 2013)).

Carandini and Heeger (Carandini et al. 2012) point out that the degree of divisive normalization is dependent upon the level of spontaneous activity (as signified in the responsiveness of the system, i.e.,., H; see above) in an area (e.g., visual cortex). Taken in a more specific way, both target and background inputs are set and compared against the level of the ongoing spontaneous activity, and encoded in relative (rather than absolute) terms based on a difference to the latter (see also (Buonomano and Maass, 2009), p.123, as well as (Northoff, 2014a), Chapters 4–5 for this point). Thus, as to be tested in the future, the level of spontaneous activity may predispose the responsiveness (i.e., H) to inputs in general, and ultimately the degree of adaptive coding in particular including input averaging and summing as described in divisive normalization (see (Carandini et al. 2012)).

Predictive coding: The concept of predictive coding is a specifically regional level coding strategy to account for context-dependence (Huang and Rao, 2011; Rao and Ballard, 1999). According to this strategy, feedback connections from a higher- to a lower-order cortical area carry predictions of lower-level neural activities, whereas the feed-forward connections carry residual errors between the predictions and the actual lower-level activities. Neurons encode differences between sample data and a prediction as predictive errors. This concept has been generalized to describe the general coding strategy of the cerebral cortex on a regional level (Northoff, 2014a; Bastos et al., 2012; Montague et al., 2006).

Predictive coding involves divisive normalization (Matsuzaka et al., 2012). Signals predicting future inputs can be conceived of as normalized outputs, as based on normalizing a positive or negative difference from background and target inputs. Analogous to adaptive coding, the generation of the predictive signals, the normalized output, may be dependent not only on the summed or averaged input itself, but also on the level of the ongoing spontaneous activity (Rigotti et al., 2013) that signifies the general responsiveness (e.g., H). Moreover, both predictive and adaptive coding share that they code neuronal activity in terms of differences between different inputs, e.g., 'difference-based coding', rather than by coding each input by itself independent of the others (as in 'stimulus-based coding') (Northoff, 2014a) Hence both adaptive and predictive coding can be thus conceived as specific subsets or instances of the more basic and fundamental coding strategy of difference-based coding.

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unaffected within this region (see Box 2 for other regions, such as the perigenual anterior cingulate cortex (PACC)) (see (Northoff and Sibille, 2014; Sibille and French, 2013; Ding et al., 2015)).

With such changes to SST interneurons the first divisive normalization stage may be expected to show abnormal summation or averaging of inputs. Specifically, inputs from different regions of the brain that process inputs from body, environment and the own self (including thoughts) can no longer be properly integrated. Accordingly, due to DLPFC deficits in SST interneurons, MDD may be characterized by a deficit in spatial input summation, whereas, based on preserved PV interneurons, output normalization may be preserved (in at least the DLPFC) (see Box 2 for discussing the specificity of changes in input and output processing in psychiatric disorders).

Spatial (and temporal) input summation or averaging as the first stage of divisive normalization may be closely related to lower frequency oscillations, such as delta and theta (see above). Abnormalities would be expected in these frequency ranges in patients with MDD, which is indeed the case, as demonstrated in various electroencephalographic (EEG) studies (Fingelkurts and Fingelkurts, 2014). This may mean that a single input is abnormally integrated into the ongoing oscillations and their temporal structure which, in turn, may hinder the integration of different inputs. Spatial and temporal input summation may become deficient with input processing focusing more on contents than context. That, as we tentatively, assume, may translate in yet unclear ways from the cortical microcircuits to the regional and network levels of neuronal activity which, analogously, may then also be characterized by abnormal predominance of content over context. The abnormal predominance of content may then be manifested in various depressive symptoms like ruminations, anhedonia, sadness, psychomotor retardation, and decreased executive function and goal orientation: the commonly underlying thread in all these symptoms is that patients are no longer able to relate their perceptions, feelings and cognitions to their respective sensory, motor, affective, cognitive, social and behavioral contexts (Fig. 3). As in schizophrenia, we thus assume that the abnormal content-context relation is transferred in yet not fully clear ways from the cellular level of cortical microcircuits over the regional and network level to the symptom and behavior level.

5. Conclusion

Neural activity in the brain at the cellular and regional levels shows strong context-dependence across domains (for example, reward, perception, decision-making and cross-modal domains) and contexts (social, cultural neuronal, behavioural and vegetative). Therefore, context-dependence is a basic feature of neural processing in the brain. The computational and neuronal mechanisms underlying such context-dependence remain unclear, however. We postulate that canonical microcircuits and divisive normalization — that is, summation or averaging inputs, and normalization of output against input — underlie the central computational mechanism that enables context-dependence at different levels and in different contexts.

Both input summation and output normalization are based on spatial and temporal integration of different inputs and output to a particular input, which accounts for the inherently spatiotemporal nature of divisive normalization and context-dependence. Divisive normalization with its two stages puts both input and output into a larger spatiotemporal context by spatializing and temporalizing them. Radically put, context-dependence may be viewed as spatiotemporal dependence or contextualization. Such spatiotemporal contextualization on the most basic level of input-output processing may be carried over to subsequent higher levels

Box 2: Specificity of changes in psychiatric disorders?

Can we characterize schizophrenia as an output normalization disorder and major depressive disorder (MDD) as an input summation disorder? Data show that in addition to PV interneurons, SST interneurons in the DLPFC may also be affected in patients with schizophrenia (Arion et al., 2015; Volk et al., 2012). Altered input summation or averaging as mediated by SST-interneurons is also supported by observations of early sensory processing deficits in auditory cortex in patients with schizophrenia (Javitt, 2009; Javitt and Freedman, 2014), which may also contribute to generating auditory hallucinations with their confusion between content and context (see above). This argues against schizophrenia being a disorder specifically and exclusively involving temporal output normalization as distinguished from spatial input summation. However, the PV interneuron deficit in the DLPFC is not observed in patients with MDD (Sibille and French, 2013; Ding et al., 2015; Northoff and Sibille, 2014) or in those with schizoaffective disorder (often also subsumed under bipolar disorder) (Arion et al., 2015). Hence, DLPFC in schizophrenia may be featured by a combined deficit of both SST-based input summation and PV-based output normalization.

By contrast, patients with MDD only show deficits in SST-based input normalization but not PV-based output normalization. However, this applies only to the DLPFC, whereas both SST and PV interneurons seem to be deficient in the PACC (Northoff and Sibille, 2014; Sibille and French, 2013; Ding et al., 2015). How does that affect the regional level of, for instance, spontaneous or resting state activity? The level of resting state activity may be a product of largely ongoing input summation with the inputs being generated mainly internally (as related to the body or the own thoughts) but also, in part, due to the ongoing externally generated sensory input (even when we close our eyes, the remaining four senses still send inputs). Tentatively, the regional differences in SST and PV deficits may then be assumed to translate into different resting state activity levels in the PACC and DLPFC, which can indeed be observed in MDD: the PACC shows resting state hyperactivity (as related to deficient input summation with preserved output normalization) while the DLPFC exhibits resting state hypoactivity (as due to deficits in both input summation and output normalization) in MDD (Northoff, 2014c).

Accounting for depression and schizophrenia (and potentially other psychiatric disorders) in terms of canonical microcircuits and divisive normalization raises a diagnostic classification question. Much recent debate has centered on how to classify psychiatric disorders (Insel et al., 2010; Insel, 2014). In the absence of well-established genetic, biochemical, and other biological markers, classification of the various symptoms has relied on a descriptive classification of diseases, as in diagnostic checklists, such as the Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

A claim has been made that the categorical symptom-based descriptive diagnostic approach should be replaced with a more dimensional transdiagnostic biologically based approach related to the impact of molecules, cells, and circuits on functions and symptoms. Such an approach has been suggested by the Research Domain Criteria (RDoC) (Insel et al., 2010; Insel, 2014). If extended to other symptoms and disorders, such as post-traumatic stress disorder (Maren et al., 2013), autism-spectrum disorder, obsessive compulsive disorder, and many others, the suggested characterization of psychiatric disorders in terms of input summation and output normalization would be in accordance with such a more biologically based approach. However, the direct relationships between canonical microcircuits and divisive normalization need to be investigated with regard to their specific spatiotemporal constellations (see above) including how these are manifest in the psychopathological symptoms requiring 'Spatiotemporal Psychopathology' (Maren et al., 2013)

of neural processing like on cellular, regional and network levels and ultimately even to social and cultural levels. Future studies are needed though to investigate whether for instance social or cultural context-dependence can indeed be traced to spatiotemporal contextualization of input-output processing.

Neuronally, divisive normalization may be realized by canonical microcircuits and their different GABAergic interneurons (SST and PV) (and possibly other interneurons like excitatory interneurons that are to be considered in the future) that establish specific input-output relationships. Importantly, different psychiatric disorders, such as schizophrenia and MDD, can be characterized by specific deficits in different interneurons within the CM which, as we will indicate in Box 2, may also depend upon the brain region involved. This leads to abnormal input summation and/or output normalization during divisive normalization, causing abnormal shifts in the balance between context- and content-dependence in these disorders as it is manifested in many psychiatric symptoms (see above).

Due to the inherent spatiotemporal nature of input summation and output normalization, their alterations may lead to changes in input and output processing with abnormal spatialization and temporalization. These changes in input and output processing may then, tentatively assumed, translate in yet unclear ways onto the regional and network level of neuronal activity as investigated with fMRI and EEG. Specifically, abnormal input summation and/or output normalization may lead to the kind of abnormal spatiotemporal activity patterns in regions and networks characterizing MDD and schizophrenia. These abnormal spatiotemporal activity pattern on regional and network levels, in turn, may then be related to the psychopathological symptoms which can then also be characterized by abnormal content-context relationship on the psychological and behavioral level. Hence, psychopathological symptoms may ultimately be traced to spatiotemporal abnormalities that are transferred from and manifest on cellular, regional/network, and psychological-behavioral levels – this amounts to what has been described as 'spatiotemporal psychopathology (Northoff, 2015a, 2015d; Northoff, 2015b, c)

5.1. Divisive normalization and coding

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Acknowledgements

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