Multilevel System Coupling of Error Commission, Detection and Correction in the Error Monitoring and Processing System are required for High Precision Task Performance, and Modulates Neural Plasticity through Changes in Glucoallostasis

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Abstract: - High precision of task performance is required in almost all activities of humans and non-human subjects – the hallmark of the functioning of the error monitoring and processing system (EMPS). In many cases, however, task precision is affected by the level of error commission, which decreases the quality of work or task performance. But error commission is an integral component of the EMPS. Previously we have estimated the physiological range of error commission to be around 5%. This suggests that above the physiological range, error commission is a n egative coupling factor in the EMPS. However, even at the physiological range of error commission, the rate of error detection and concomitant correction, which are required to improve task precision, differs in many subjects. In conditions of correct performance of task, precision is promoted, and thus, represents a positive coupling factor in the EMPS. Therefore, error commission, detection and correction represent integral components required for high precision task performance. Been the main energy substrate for neural activity, glucose modulates several domains of EMPS. Interestingly, the main components of EMPS functioning – error commission, correction and detection are associated with changes in glucoallostasis. Here we propose the high precision functioning of EMPS involves coupling at different levels of error commission, correction and detection. Further we suggest that this multilevel coupling modulates neural plasticity through changes in glucoallostasis. This work provides a conceptual background to the modeling of high precision task performance in human and non-human subjects.

1 Introduction

Error commission, detection and correction constitute the integral products of the overall activities of a monitoring response system located in the mediofrontal brain – referred to as t he error monitoring and processing system (EMPS). The EMPS is a complex neural network diffusely located in different brain regions and is responsible for error commission, detection, and correction. These three generic components provide important

cue to the state and functioning of the EMPS. They are influenced by both endogenous and endogenous factors. In a previous paper [1] – [3], we examined the effects and possible mechanisms of glycemic allostasis (glucoallostasis) on this system. The effects of other substances such as alcohol have been examined by our group [4], [5] and also reported elsewhere [6] – [10]. In this paper, we aim to ascertain the levels of interaction amongst the generic components of the EMPS. On the basis of our data as well as new research evidences, here, we propose that each integral component of the EMPS functions as a sub-system, but coupled to each other via multilevel interactions, in particular through glucoallostasis. This coupling is required to ensure optimal level of precision of task performance, a necessary factor in everyday life of both human and non-human subjects. Further, we suggest that the coupling of the sub-systems of the EMPS modulate neural plasticity through changes in glucoallostasis.

2 Error Commission, Detection and Correction Sub-systems as Integral Components of the Error Monitoring and Processing System (EMPS) are Coupled to each other by Complex Neural Connections

Error commission can be defined as the deviation from set goals occurring when subjects, for instance, in an experimental condition deviate from the set goals, and is accompanied by reduction in task precision. Error commission is related to the functions of the monitoring response system in the mediofrontal brain precisely in the substantia nigra of the midbrain, basal ganglia and cortex of the forebrain and is dependent on the degree of phasic dopaminergic activity on the ACC. (other regions of the brain have been implicated in EMPS activity) [11] – [15]. The error commission activity of this response system is evident in the amplitude of the Error Related Negativity (ERN) or Error Negativity (Ne) (ERN=Ne) [16], [17]. The ERN is a negative deflection having its maximum in the midline of the frontocentral region of the scalp, noticed around 50–150 ms in course of EEG (electroencephalogram) recording, and occurs when subjects commit error in an experiment [18].

It is unlikely that the ERN waves are associated with error commission alone. Ref. [19] reported small ERN wave on correct response trials in a cognitive task, suggesting that this wave component of EMPS may be related to other domains of EMPS

activity including error correction, detection as well as associated systems of error processing and monitoring (e.g. affective dimensions). In fact, relatively recent findings suggest that error positivity, another integral component of error processing and monitoring is associated with error commission and detection [20]. Researches have shown that in cognitive tasks, error commission is usually followed by post-error adjustment, which comprises post-error slowing and post-error improvement of task accuracy and precision. This adjustment is an intrinsic function of the neural network of the EMPS aimed at reducing the likelihood of occurrence of a second error. The mechanisms for these processes are thought to involve cognitive and behavioral systems with differential activation and inhibition of neural networks in specific regions of the brain as well as modulation of the activity of the readiness potential (Bereitschaftspotential) [21], [22].
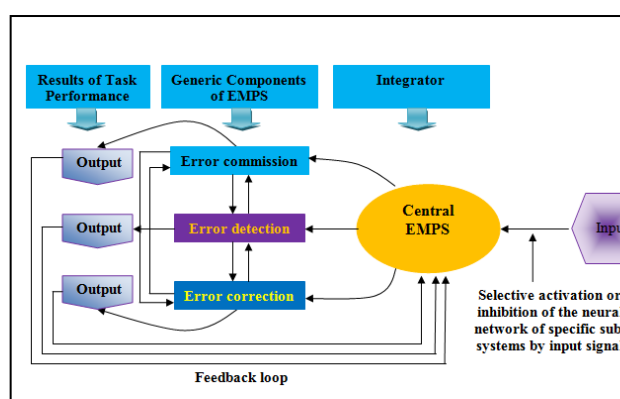

Fig. 1. Multilevel subsystem coupling in the error monitoring and processing system (A)

The data from our investigations [4], [5] and those of other authors [23] – [26] indicate that immediately after error commission, some subjects are able to detect and then correct the error, suggesting that error commission, detection and correction are interlaced and coupled to each other via neural networks as well as biochemical coupling that seem to evolutionarily enhance task precision. (Fig.1. is a schematic representation of such a coupling). This neural coupling of task ensures that cognitive tasks are executed with high precision. Malfunctions in this coupling are the cause of error monitoring and processing disorders observed in many activities of humans resulting to the loss of lives and properties [1] – [5], [27], [28]. In some brain pathologies such as Parkinson's disease, schizophrenia, personality disorder subjects are unable to complete a cognitive task successfully or

complete it with disordered monitoring and processing with associated disordered signaling of neural network of EMPS [29] – [32]. Importantly, substance use has been implicated in disordered signaling of this neural network of error monitoring and processing [33], [34].

3 Multilevel System Coupling of Error Commission, Detection and Correction in the Error Monitoring and Processing System are Required for High Precision Task Performance

High-precision error coupling is the hallmark of EMPS functioning that is the result of effective neural processing and monitoring of error signals at different levels of error commission, detection and correction. The coupling of error signals at different levels of EMPS is required for precision of task performance. Though numerous factors such as alcohol and neurobehavioral diseases affect task precision by influencing the neural network of EMPS (and associated systems – behavioral and cognitive) and metabolic competency of the neural cells associated with EMPS, ongoing investigations in different laboratories around the globe are aimed at reducing error and increase precision of performance of humans and non-human subjects [35]. The factors that negatively affect the EMPS activity have been constantly implicated in catastrophic cases including motor vehicle, air, industrial, and engineering disasters as well as in medical tragedy [36] – [38]. Hence the need for continued research on the modalities required for improvement of performance and quality of work execution. This is of immense social and economic relevance [35].

High precision of task performance is, at least, in part, due to the coupling of the different components of error processing and monitoring, which occur through the multiple neural associations between different levels of brain functioning. Though the relationship between the different components of the EMPS is not exactly understood, multiple, but similar brain regions are believed to control all three components of error commission, detection and correction. For instance, the anterior cingulate cortex (ACC) and prefrontal as well as dopaminergic brain regions are responsible for error commission, detection and correction. Error commission by subjects in an experiment evokes increased activity in these brain regions. However, correct responses elicit increased activity in the

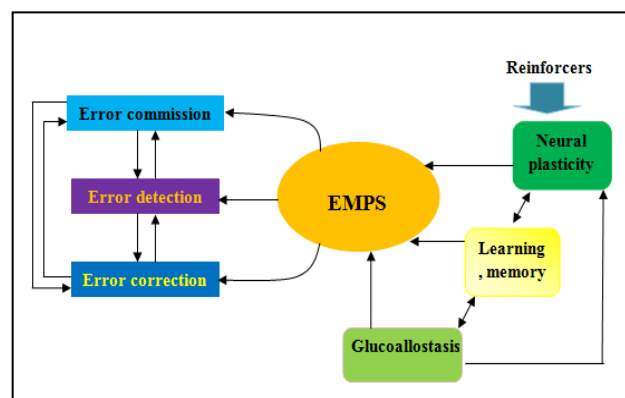neural networks of some areas of the prefrontal cortex, striatum, and cerebellum [2] – [33].

Fig. 2. Multilevel subsystem coupling in the error monitoring and processing system (B)

# 4 Error Coupling in the EMPS Modulates Neural Plasticity through Changes in Glucoallostasis

Like any other neural process, error processing and monitoring involves numerous levels of interactions at the cellular and molecular levels. A couple of investigations have reported transcriptional changes associated with the neural network involved in EMPS functioning, and associated systems of memory and cognition [39] – [42]. The multilevel system of EMPS involved in error coupling actively modulates neural plasticity, at least, in part, through glucoallostasis regulation [1]. (Also see Fig. 2). This occurs via the influence of EMPS activity on the signaling cascades of transcription factors (e.g. Fox, CREB, NFAT), growth factors etc. (Fig. 3). These factors signal downstream the nucleus and interact with gene expression [43] – [49], and also have epigenetic effects on membrane transporters of glucose and the enzymes and molecular sensors of energy allostasis [33]. Other associated mechanisms in these processes include activity-induced plasticity, nuclear translocation, and long-term potentiation [45], [49].

To reiterate, neural cells (including those of the EMPS) are primarily dependent on glucose as their metabolic substrate. Dysregulation of glycemic levels is associated with dysfunctions of error processing and monitoring [1] – [3], [33]. Both availability and utilization of glucose by cells of the EMPS that ensure their adequate functioning, under conditions of maintenance of glycemia within normal range under a variety of stressors are necessary to maintain the structural and functional architectural integrity of cells of the neural network

of EMPS and associated systems. Error commission, detection and correction are coupled by multiple mechanisms at different levels of the neural network responsible for the monitoring and processing of error (Fig. 2 & 3). Indeed precision of task performance is characterized by certain degrees of neural signaling in specific regions of the brain, controlled by multilevel mechanisms and interactions that modulate neural plasticity through changes in glucoallostasis. The term "glucoallostasis" (glycemic allostasis) refers to the process by which blood glucose stabilization is achieved through the balancing of glucose consumption rate and release into the blood stream under the action of a variety of stressors. Maintenance of glucoallostasis involves multiple regulatory systems at the peripheral and central levels. It involves glucose acting as a peripheral signal for the secretion of the respective hormones and mediators primarily by pancreatic endocrine or other cell types. Adequate glucoallostasis regulation is essential not only for EMPS functioning, but also cognitive functioning. Unfortunately, however, little attention has been given to the allostatic regulation of glucose that ensures adequate functioning of EMPS and associated systems [1] – [3]. We assessed the influence of long-term (duration of 6 hours) cognitive load on glycemic allostasis and error processing/monitoring (on fasting) in healthy volunteers who were either total abstainers or alcohol users who had had their last episode of alcohol consumption since the past 7–28 days prior to the experiment. In our study, involving 27 volunteer participants (abstainers, n=8; sober participants, n=19), it was observed that the rate of error commission, for instance, was higher in subjects who consumed alcohol compared with the total abstainers. The blood glucose levels over the period of the experiment were significantly higher amongst the total abstainers compared to their sober counterparts. The baseline value of abstainers was 4.24±0.19 mmol/l; for the sober – 4.54±0.15 mmol/l. The average rise in glycemic levels in the abstainers was +0.67±0.08 mmol/l (p<0.05; t=8.375) after 2 hours, +1.16±0.17 mmol/l (p<0.001; t=6.824) after 4 hour s and +1.54±0.16 mmol/l (p<0.001; t=9.625) after 6 hours of intensive mental (cognitive) performance on f asting. In the sober subjects increase in blood glucose level was observe only after 2 hours of cognitive performance on fasting (+0.28 mmol/l, p<0.02). Further analysis showed that glycemic levels in these subjects was – 0.01 mmol/l after 4 ho urs and –0.55 mmol/l (p<0.05) after 6 hou rs. The glycemic level at 6 hours in the sober subjects corresponded to

functional relative hypoglycemia. The negative influence of alcohol on glycemic level ranged from 18.1% (r=-0.425; p=0.027) to 64.8 % (r=-0.805; p<0.001). Our calculation also reveal that the contribution of glycemia to cognitive functions was 11% (p<0.05) – 39% (p<0.001). Importantly the level of glycemia also had substantial effect on the level of error commission. The level of error commission among the abstainers remained stable in course of the study and did not exceed 5% of the baseline. The error commission rate of the alcohol users increased significantly from 3 errors after 2 hours to an average of 18 e rrors after 6 hou rs of intensive cognitive load. This biochemical coupling of the EMPS to task precision is associated with substantial changes in the activity of neural cells that comprise the EMPS and associated systems – which in turn can modulate neural plasticity.

Fig. 3. Multilevel subsystem coupling in the error monitoring and
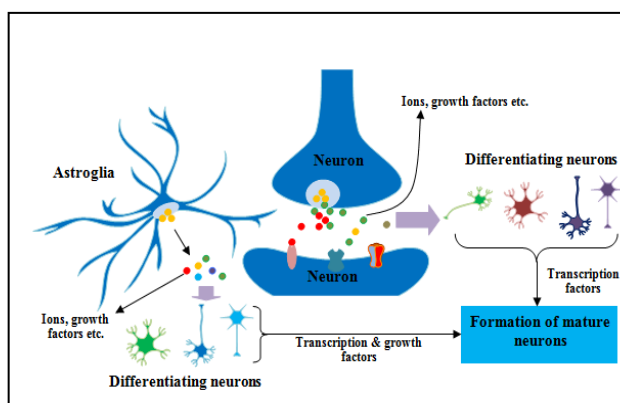
processing system

The term "neural plasticity" (or neuroplasticity) was first used by William James to denote changes in neural pathways that were associated with some forms of learning and memory [50]. Further development of the concept of neural plasticity was made during the close of the 19th century and the first decade of the 20th century by Eugenio Tanzi, Ernesto Lugaro, Ramon y Cajal independently indicating the role of learning, memory, practice, and experience in changes associated with structural and functional architecture of neural and synaptic connections in daily activities of humans and across the life span of an individual [51]. Other notable pioneers in neural plasticity were Konorski and Hebb among others [50]. Neural plasticity is the ability of the neural wiring of the brain (and other regions of the nervous system) to respond to intrinsic or extrinsic stimuli by reorganizing its microcircuitry with corresponding impact on functions [52]. It is a prerequisite for livings

systems to adapt to the environmental changes, occurring during lifetime [53]. Numerous factors influence neural plasticity. These factors include cognitive activity, exercise, caloric restriction, experience, pharmacologic agents, ageing, neurobehavioral diseases such as Parkinson's disease, drug (alcohol, cocaine, amphetamine) abuse etc. [45], [52], [53] – [56]. It should be mentioned that changes in neural plasticity may be accompanied by either positive or negative influences on EMPS functioning or cognition [55]. The mechanisms of neural plasticity are not completely understood. But studies suggest that plasticity of neural network involve the activities of several neurotransmitters/neuropeptides and their receptors (such as g lutamate, dopamine, GABA, AMPA receptors), as well as trophic factors (such as the brain derived neurotropic factor) [54], [55]. Neural plasticity has been associated with *c fos* expression, a transcription factor that is affected by alteration in the neural circuitry of error processing and monitoring [57]. The level of activity in the neural system itself also impacts on neural plasticity (termed activity dependent changes in neuroplasticity) [53]. Numerous regions of the brain (including those involved in EMPS functioning) have been implicated in neural plasticity. These regions include the prefrontal cortex, nucleus accumbens, and ACC [45], [55], [56].

4 Future Directions

Since the functioning of EMPS and cognition as well as neural plasticity are interlaced at some levels of neural signaling (and particularly through glucoallostasis), it is important to investigate the primary and precise mechanisms that couple these different components of error processing and monitoring to effectiveness in cognitive monitoring. This may provide useful information on some of the modalities in improving task or work performance.

4 Conclusion

The integral components of EMPS are coupled to each other via neural networks that mediate multilevel interactions with other systems via multilevel interactions. The activities of EMPS, cognition and neural plasticity are interlaced at some levels of neural signaling, and are also related to each other through glucoallostasis regulation. This coupling is required to ensure optimal level of precision of task performance, a necessary factor in

the everyday life of both human and non-human subjects.

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