Neurophysiological circuits involved in the Problem-Based Learning method: bridging neuroscience and education

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RESUMO

Introdução: A aprendizagem baseada em problemas (PBL) é um método de ensino no qual os alunos são levados a aprender por meio da resolução facilitada de problemas guiada por um professor. Nessa metodologia de aprendizagem, o professor assume a função de tutor e os alunos colaboram em pequenos grupos que trabalham para identificar o que precisam aprender. Nossa hipótese é que a metodologia PBL estimula o recrutamento de áreas cerebrais para alcançar a aprendizagem substanciada pela montagem de circuitos neurofisiológicos. Este artigo tem como objetivo considerar cada etapa da metodologia de ensino do PBL e conectá-la aos neurocircuitos envolvidos, com base na literatura atual da neurociência. Uma análise para cada etapa do PBL inclui seu papel central nos processos de aprendizagem e explora sua base nos circuitos do cérebro, como memória e plasticidade neural. **Material e Métodos:** Literatura e teorias foram revisadas para elaborar conceitos pertinentes em PBL e os neurocircuitos envolvidos. **Discussão:** Atualmente, a conexão entre esses dois campos é mal abordada na literatura, e há evidências significativas de que cada etapa do PBL envolve unidades de neurocircuito bem estudadas. **Conclusão:** Por meio de suas sete etapas sequenciais e aquisição de conhecimento em espiral, o método PBL está empenhado em motivar os alunos a se tornarem bons alunos e, consequentemente, fornecer a chave para um desempenho sólido e proativo. Isso é substanciado pelas extensas conexões que podem ser feitas dentro de cada etapa da PBL e da literatura da neurociência. Nesse sentido, alguns pontos da presente metodologia são viáveis para uma exploração posterior, a fim de explorar a provável relação entre neurocircuito e aprendizagem.

Palavras-chave: Aprendizagem baseada em problemas (PBL), memória, aprendizagem, habilidades cognitivas, circuitos neuronais.

ABSTRACT

Introduction : Problem-based learning (PBL) is an instructional method in which students are driven to learn through facilitated problem solving guided by a teacher. In this learning methodology, the teacher assumes a tutoring role and the students collaborate in small groups that work to identify what they need to learn. We hypothesize that the PBL methodology stimulates the recruitment of cerebral areas to reach substantiated learning by assembling neurophysiological circuits. This paper aims to consider each step within the PBL teaching methodology and connect it to the neurocircuitry involved based on current neuroscience literature. A breakdown for each PBL step includes its pivotal role in the learning processes and explores its foundation in the brain circuitry, such as memory and neural plasticity. **Material and Methods:** Literature and theories were reviewed to elaborate pertinent concepts in PBL and the neurocircuitry involved. **Discussion:** Currently, the connection between these two fields is poorly approached in the literature, and there is significant evidence that each step of PBL involves well-studied neurocircuitry units. **Conclusions:** Through its sequential seven steps and spiral-like knowledge acquisition, the PBL method is committed to motivating students to become good learners and, consequently, to provide the key to solid and proactive performance. This is substantiated by the extensive connections that can be drawn within each step of PBL and neuroscience literature. In this sense, some points of the present methodology are feasible for further exploration in order to explore the likely relationship between neurocircuitry and learning.

Keywords: Problem-based learning (PBL), memory, learning, cognitive abilities, neuronal circuitry.

INTRODUCTION

Problem-Based Learning (PBL) is a teaching method that has increasingly been used with undergraduate students, especially in medical education worldwide[1]. In contrast to the traditional Lecture-Based Learning (LBL)[2,3], in the PBL method, the students construct their learning under the guidance of a teacher, usually referred to as a tutor or facilitator. PBL is an active learning pedagogy that fits the modern concept of learning (Figure 1). It is constructivist, contextual, promotes knowledge sharing and self-directed study[4-6].

The central stimulus to learning through PBL is the tutorial session[7], where a small group of students and one tutor meet and solve a problem, usually a clinical case, every week during the preclinical stage of a medical course[8]. In this constructive learning process, PBL principles are systematized in 7 cumulative steps[1] distributed in tutorial sessions that runs in two parts[9], in which students engage in self-directed learning to solve a strategic problem, reflect on what they learned, and evaluate the effectiveness of the strategies they employed (Figure 2).

During the first part, students identify gaps in their knowledge regarding the subject under discussion and establish learning goals necessary to acquire the necessary knowledge to solve a problem. Following a self-study period, usually one week, the students and tutor meet again to finalize the process. By critically discussing the new information in a problem-solving process context, each student shares the acquired knowledge related to the problem with the group to enrich its knowledge[5].

In the second part of the tutorial session, under the tutor's guidance, the students share the knowledge they acquired by self-study following the previously established learning goals. The sharing of knowledge allows students to reconstruct their pre-existing mental map into a productive model that will be useful in solving and making predictions regarding future problems and phenomena. Collectively, all these steps will lead to strong memory retention and restructuring of thinking, thus generating knowledge favoring spiral-like knowledge acquisition[5,10].

We hypothesize that with each step, PBL methodology stimulates the recruitment of cerebral areas to reach substantiated learning; indeed, this relationship can be explored in order to assemble the neurophysiological aspects of the learning. This manuscript intends to present an approach of the neurophysiological circuit based on the PBL processes as a teaching methodology based on the scientific literature in neuroscience and education.

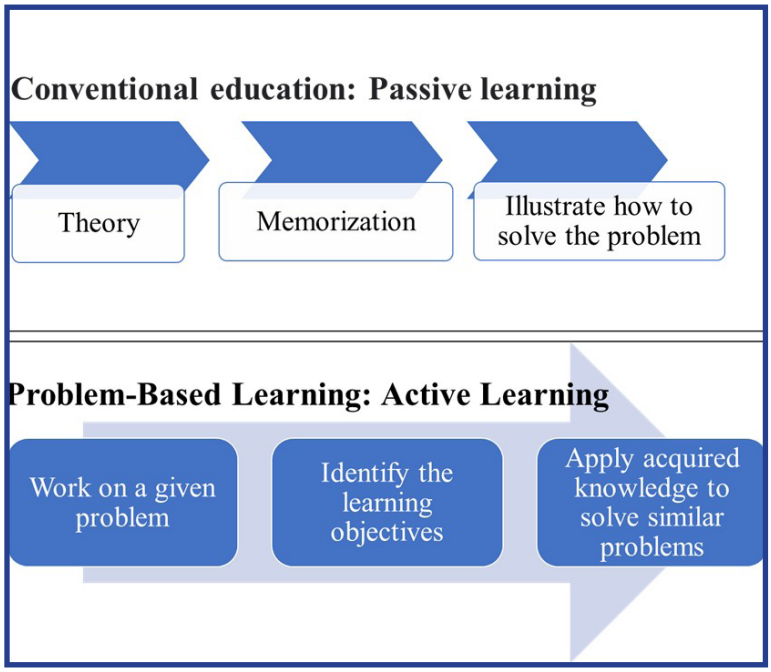

Figure 1. Conventional education: Passive learning vs Problem-Based Learning: Active Learning.

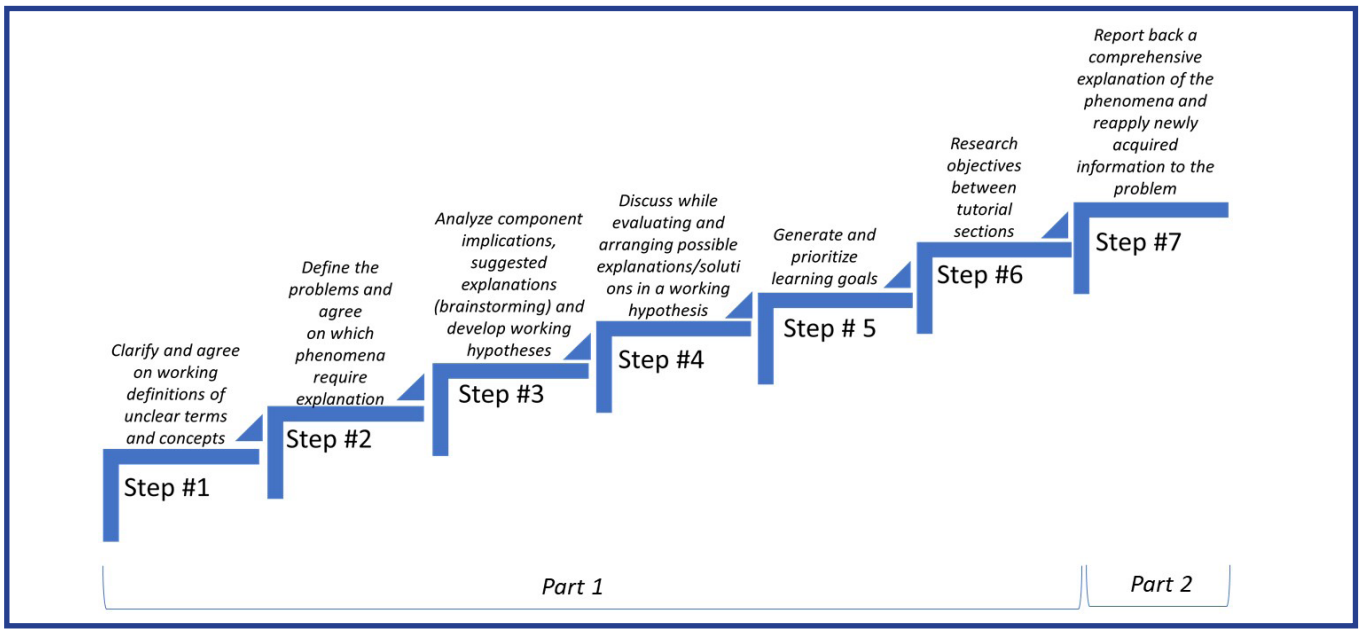

Figure 2. Problem-Based Learning (PBL): 7 cumulative steps distributed in tutorials sessions..

METHOD

We conducted searches through the following databases: PubMed, EMBASE, Web of Science. There were no temporal limitations. We focused on full-text articles independent of the type of publication. No language restrictions were applied. The search was driven by the following keywords alone or matched with the Boolean operators "AND" or "OR" were: Problem-Based Learning / PBL; Neuronal circuitry; Memory, Learning, Cognitive abilities.

RESULTS

Background "problem" in PBL as a neurophysiological key

The foremost idea in the PBL scaffold is that the preliminary point for learning must be a problem, which the learner becomes motivated to solve[11,12]. In the learning process, the relevance of having a functional problem[13] is based on the neural substrate interaction required during the cognitive control stimulated by tools such as abstract rules, a new situation, or task-sets needed for cognitive control. The new situation is supposed to be a "problem situation," which will be developed along with the seven steps of PBL (Figure 2).

Executive functions (searching for responses) and learning share common neural substrates essential for their expression, notably in the prefrontal cortex and basal ganglia[14].

Vaishnav et al[15] demonstrated that incorporating meta-cognitive learning practices in medical education offers a basis for enhancing teaching, making it learner-centric[15]. Through the active learning process of PBL, there are interactive engaged cognitive control and learning to develop long-term, rather than short-term, memory. One focal point of PBL curriculums is based on cumulative learning, which directly depends upon memory storage. PBL structure is frequently systematized in a spiral way, a concept attributed to Jerome Bruner[16]. Based on Bruner's postulation, the "spiral of learning" consists of an integrative revisiting of topics, subjects, or themes throughout a course[16]. It is not a simple repetition of a taught issue, but the incremental increase of learning, with each successive encounter building on the previous one[17].

Memory is a necessary attribute in the success of knowledge-based learning and involves neural plasticity. The main categories of memory are conscious/declarative (explicit memory) and unconscious/nondeclarative (implicit memory)

(reviewed by Kandel, Dudai, Mainford[18]). The former involves neural circuitry acquirement, maintenance, and expression (the usage) of learned knowledge, which depends on the hippocampus and adjacent cortex. The latter is mainly due to the cerebellum, striatum, and amygdala involving mechanisms of acquirement and maintenance information in short- intermediate- and long-term memory, respectively[19-24].

Memory categorization[25] should be considered a link of learning in order to understand the effectiveness of PBL better. Categorization of learning[26] depends on the recruitment of a variety of systems to reach neural plasticity, including neocortical regions, the medial temporal lobe, the basal ganglia, and midbrain dopaminergic systems[27].

Plasticity and learning in PBL

A key issue in learning is the requirement to balance the advantages and disadvantages of different kinds of plasticity (fast vs slow).

The output of the hippocampus trains slower local cortical networks to link new memories to old memories, resulting in long-term memory consolidation in the neocortex. Long-term memory consolidation results from fast plasticity in the hippocampus[27]. An interaction between fast plasticity[14] (in the basal ganglia) and slow plasticity (cortex) underlies many forms of category learning and elaboration. In PBL, the tutor facilitates knowledge construction[7,9] as part of neural plasticity, stimulating previous knowledge and elaborating new information.

Considering PBL, we suggest the cyclic activation of hippocampal cells as the most promising route involved in the process of knowledge acquisition[28]. To support our idea, the most prominent proposal implies long-term potentiation (LTP)[29] as the mechanism underlying rapid hippocampal plasticity[28]. Cells in the neocortex that represent an event are activated and, in turn, stimulate hippocampal cells. Cyclic activation of neocortical and hippocampal cells is needed to establish the memory trace. Repeated retrieval of an event over time will strengthen the connections between the neocortical cells that represent the event, eventually eliminating the need for the hippocampus to link them together[28].

Another proposal is that the hippocampus acts as a memory "index"[30]. The neocortical cells, in turn, activate a group of hippocampal cells that become linked together. These hippocampal cells then act as a retrieval index for the original pattern of cortical activation. This theory presupposes specific bidirectional connections from the hippocampus to the cortex. With respect to consolidation, it is widely accepted that the hippocampus might periodically reactivate the cortical representation, which would then change over some extended time period[28,31]. For PBL to be considered successful, confronting new knowledge with knowledge previously acquired is an essential stimulus to memory consolidation in the process of activation–elaboration[32].

Additionally, concerning the long-term potentiation form of activity-dependent plasticity due to a persistent enhancement of synaptic transmission and synapse-specific plasticity, NMDA (N-methyl-D-aspartate)[32,34] receptor activation is critical to induce synapse-specific plasticity within both the hippocampus and amygdala[34]. Calcium/calmodulin-dependent kinase II (CAMKII) stands out as a key player for initial memory formation[35-37].

An essential key in this long-term potentiation (LTP) of synaptic plasticity is a brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin, and its signaling depends on MAPK (mitogen-activated protein kinase)[38] and CREB (kinase cascade activates gene transcription dependent on the cAMP-responsive element-binding protein) – both of which are indispensable for long-term memory signaling[37,39-44]. According to Steward and Schuman[45], and reviewed by Gieze and Mizuno[37], BDNF can induce local translation of dendritically targeted mRNAs. It raises the possibility that neurotrophins can act in concert with activity-dependent increases in mRNA levels to affect synaptic efficacy. BDNF released during intense synaptic activation could provide a mechanism for prolonged[46] augmentation[47] of NMDA currents or other factors regulating synaptic translation[48] in the absence of repeated episodes of high-frequency activity. Such a role for BDNF is likely to be involved in several synaptic and behavioral patterns of memory consolidation[49].

The neurophysiology of active learning is inherent to PBL

Memory storage is not simply a linear

achievement toward the permanent long-term memory. Still, it depends on the dynamic and interactive processes[50, 51] to encode issues already learned or new information acquisition, involving both short- and intermediate-term memories, and to consolidate and maintain long-term memory[18].

Being interested in examining event-related brain potential (ERP) Voss, Galvan and Gonsalves[52] hypothesized the following conditions: i) active learning involving the self-generation of complex action sequences and behavioral strategies and ii) passive learning intended to severely restrict the self-generation of these action sequences and strategies. The teaching object in PBL is the problem to be solved, which boosts the active-learning strategies through action planning, allowing rapid reactivation during memory retrieval[52].

The advantage of active learning is partially due to the implementation of simple behavioral strategies[53]. We know that regarding PBL, strategies are correlated with the collaborative and self-study-centered approaches, so the active learning, inherent in PBL, is correlated with brain activity in a widespread network of prefrontal, parietal, and hippocampal visual-processing regions. Kim[54] demonstrated, by a meta-analysis, a study of brain activity during memory encoding. His work presented the involvement of the bilateral medial temporal lobe (MTL), the left inferior frontal cortex, the bilateral fusiform cortex centered on the intraparietal sulcus, and the bilateral posterior parietal cortex. Additionally, a review by Bloom and Doss on creativity suggests that engaging in creative tasks, such as active learning in PBL, positively affects the brain by elevating feelings of happiness and reducing anxiety[55]. Ergo, we suggest that neurological findings, such as those made by Kim[54] and Bloom and Doss[55], are important to consider when engaging students in the PBL learning process.

DISCUSSION

The Seven Steps in PBL

This section will consider each of the 7 steps in PBL (Figure2) and discuss the currently accepted neurocircuitry (Figure 3) related to each respective step in the learning process.

Clarify and agree on working definitions of

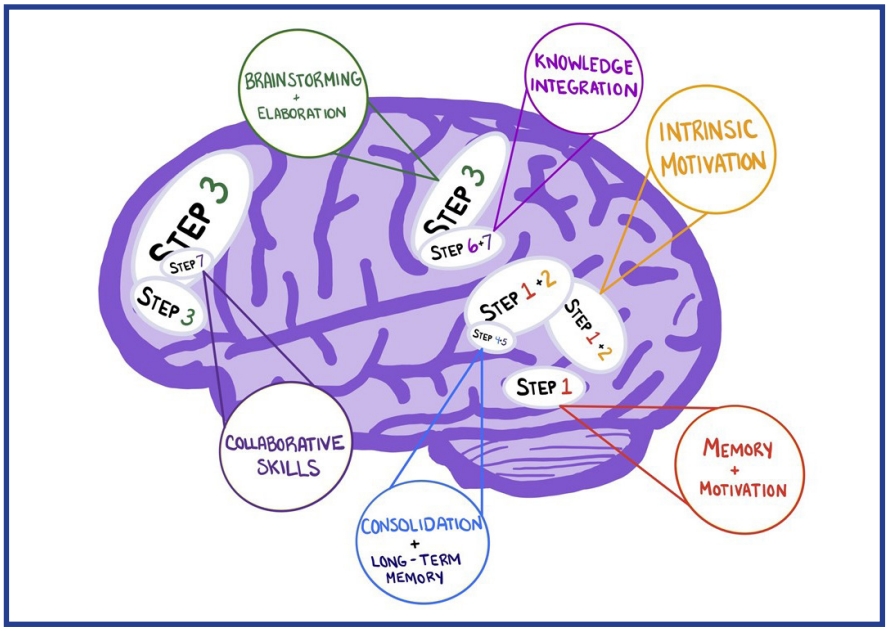

Figure 3. Schematic representation of brain areas (Brodmann areas) recruited according to PBL steps. Steps 1 and 2: clarifying and agreeing on work definition of unclear terms (occipital and temporal areas); Step 3: Start solving problem evaluation and hypothesis testing; Step 4 and 5: integration with topics previously discussed; Step 6: abstraction and elaboration - self-directed learning. Step 7: solving problem – learning structuration of newly acquired information to solve the problem/ long-lasting memory. We propose that PBL methodology stimulates gradual and crescent recruiting cerebral areas to reach the substantiated learning. PBL may lead to solid memory retention and restructuring of thinking, thus generating knowledge supporting spiral-like knowledge acquisition.

unclear terms and concepts (step #1) and Define the problems and agree on which phenomena require explanation (step #2).

In a given problem of PBL, new terms or new words are subject to a wide variety of plausible alternative interpretations[5]. This contextualization is incited by new word[56] learning or applying it to an unknown context in the first step of PBL. Our assumption is based on the fact that these areas process sensory information in the extrastriate cortex (Brodmann areas—BAs—18 and 19)[57] and the fusiform gyrus (BA 37). These areas are involved with recognition, imagery and elaboration of visual inputs, as well as Wernicke's area (BA 22) for analysis and elaboration of syntax of auditory information[58].

Motivation (intrinsic motivation) is a relevant point regarding step#2, which in turn can be linked to self-directed learning[11,59].

The PBL approach puts together both content and thinking strategies for problem-solving. Around this concept, it is assumed that motivation to detect the learning objectives may be one crucial driver. In PBL, there are complex problems with no single correct[60] answer. PBL's structure aims to engage students to effectively collaborate[61] in self-directed learning[62] employing intrinsic motivation[63-65]. Prior knowledge activation and contextualization61 increase in importance from the next step.

Any instructional approaches based on a problem offer the potential to help students develop flexible[66] understanding[67] and lifelong learning skills. Indeed, there are links between the neurophysiology of learning and the motivational circuitry to long-term memory1[1].

The dorsal neostriatum generates motivation, and the dynamic limbic transforms learned memories into motivation[68]. The psychological motivation value of previously acquired memories leads to changes in the mesocorticolimbic circuitry, driving to learn something new[68].

The activation of mesocorticolimbic circuits is via neurons belonging to the nucleus accumbens (NAc) (especially rostral shell), the prefrontal cortex, the ventral pallidum, and the ventral tegmentum, and triggered by a re-encounter with a novel physiological stimulus, mainly a sensitive stimulus[69]. In these steps of PBL (#2 and #3), these stimuli can be listening to their peers questioning the content of the problem or reading words they identify as unfamiliar.

Analyze component implications, suggested explanations (through brainstorming) and develop working hypotheses (step #3)

The tutor integrates new incoming information with an appropriate knowledge base to guide students[61,70,71]. It has been proved that knowledge is significantly improved when abstraction is achieved independently of a context (problem). When knowledge is restricted to a specific context[72,73] in which it was learned, deficiencies in knowledge acquisition are likely to occur. On the other hand, it is significantly improved when elaborative behavior is stimulated by adequate neural circuitry[74]. Problematized learning cannot be effective if the learner has not stimulated the neural circuitry leading to the elaboration[61,62,75, 76] necessary to consolidate the memory.

The brainstorming activity drives students to ponder their own theories while providing opportunities to make mistakes[77,78] that will be realized upon reading and generate a "painful" stimulus when processing the elaboration. This was further elaborated on by Terry Barret[79], who described students' feelings about PBL, which included the sense of "fear." Based upon the data assembled on the current review, this fear should not be interpreted as a negative but as the discomfort that stimulates the learners to solve the problems on unfamiliar topics. The lack of knowledge becomes the trigger that boosts searching for answers. The neurocircuitry associated with this discomfort can be traced back to a threatening stimulation that leads us to survive rather than get stuck/freeze.

According to Kelly et al.[80], retrieving memories of painful events activates the anterior cingulate cortex and the inferior frontal gyrus. Indeed, to localize the central circuitry, the stimulus one should use to compare the neural components activated during the brainstorming is 'pain'[81,82]. The causation of pain induces intermediate memory formation[82], which can be converted into long-term memory by spaced repetition. Suppose pain causes the stimulation of a facilitator presynaptic terminal at the same time the sensory terminal is stimulated. In that case, there is serotonin release at the facilitator synapse on the sensory terminal's surface[83]. Learning is closely associated with modifying the communication

between the neurons structuring synaptic plasticity to acquire, store, and recall information. If, during the discussion84, it becomes necessary to recall facts and events, i.e. declarative memory, the medial temporal lobe (MTL)[85] will afterward be accessed to connect to specific areas in the cortex (the prefrontal and posterior parietal cortexes). During this step, the students frequently try to recall subjects recently learned. Thus, MTL is an essential structure due to its relation to recent and temporary memory[32].

When processing information in the MTL, the hippocampus is the ultimate recipient of convergent projections from the perirhinal cortex, parahippocampal cortex, and entorhinal cortex[86]; however there is a functional division arising from the MTL localized between the hippocampus and around the medial temporal lobe cortex (MTLc) as attributes of memories[87]. MTL and basal ganglia are engaged differently during classification learning depending upon whether the task is emphasized as declarative or nondeclarative memory - even when the to-be-learned material and the level of performance did not differ[88]. We propose that the brainstorming stimuli progress to motivation with continuous PBL practice. Orchestrated by the cholinergic–dopaminergic reward systems, the sense of familiarity that comes with new knowledge would replace the previous "painful stimuli" neurocircuitry. This transition takes the students to the next level: the readiness to practice this active learning method corroborating for long-term memory retention (further discussed - "steps #6 and #7").

In this sense, we assume that elaboration involving constructing and reconstructing students' knowledge networks improves to the same extent as the robustness of the brainstorming session.

Discuss while evaluating and arranging possible explanations in a working hypothesis (step #4)

The goals of this step are usually summed up by drawing a web diagram (flowchart)[89], to link similar information and separate unrelated topics, just like one of the functions of the hippocampus. This is the consolidation: new and old information are compared to find similarities and differences; the comparison is stored where it's directly associated with related memories. Therefore, the hippocampus implements pattern separation, which aids the memory searches performed by the thalamus[90].

Although the pattern separation in the learning process starts at the 4th step, it will be established in the 5th step because the areas of the brain involved in this pattern are associated with an organizational circuitry that allows students to make productive connections between important mental stored topics.

A flowchart stimulates the visual cortex, which exhibits profound plasticity during development[91]. The interaction of glutamate[92,93] on its neuronal receptor is the signal to trigger a cascade of downstream synapses[94] involving PKA (Protein Kinase – A). This interaction is a well-explored neurophysical phenomenon that can explain the connection between visual stimuli and learning.

Reading the problem situation (during step #1), the respective listening, and the writing of the flowchart (during the 4th step) are considered sensory stimuli, triggering synapses in neural circuits. The pathway regulating neural circuits in sensory cortices is assumed to process learning-induced plasticity[95].

In PBL, the group discussions and the self-explanations elicited improve understanding[78]. Since regulations of the sensory stimuli are important while determining the role of sensory systems in cognition, the students' collaborative performance, as seen in PBL[96], is crucial to stimulate neuronal synapses and their respective plasticity. Group activity involves both social interaction and behavioral performance. Also, it depends on AVP (arginine vasopressin) synthesized in the paraventricular and supraoptic nucleus of the hypothalamus acting on limbic areas, including the hippocampus by interneuronal communication via the V1A-Gq receptor[97]. AVP enhances learning and memory by facilitating consolidation and recovery processes operating in parallel with LTP mechanisms. AVP is responsible for autonomic and metabolic changes, thus linking attention, emotion, learning, memory, and behavioral performance to information acquisition[81].

Generate and prioritize learning objectives (step #5);

From this step, the pattern separation, which was in progress, becomes evident in the neurophysiological circuitry stimulated by PBL. Pattern separation will be completed before the start of step #7, while pattern completion will be

established at the end of step #7.

The arrangement between separation and completion patterns is related to the activation of encoding vs. retrieval modes while learning takes place[98,99]. The pattern separation activity is associated with the CA3/dentate gyrus region, and it is consistent with pattern completion in the CA1 and the subiculum regions[100].

The long-lasting synaptic strengthening involves CaMKII101, extracellular signal-regulated kinase 1 and 2 (ERK1/2), and tyrosine kinase acting on the hippocampus. Long-term memory formation ERK1/2102 also activates transcription dependent on CREB (cAMP-responsive element-binding protein)103. Since this LTP is a stable form of memory, such pathways are associated with effective learning systematized during each PBL step. This is one of the cellular pathways for encoding (to convert information into a knowledge structure), storing (to accumulate blocks of information), and retrieval (recall things we already know)[28,86,87,104].

Research objectives between tutorials (step #6)

Issues already learned greatly influence the ability of the brain to capture and store new information. Subjects learned are spontaneously reactivated and strengthened in the brain during rest periods, such as sleep, but also the prospective benefits of spontaneous offline reactivation for future learning are essential. This reactivation and interregional coupling are supported by the ability to learn related content in later situations[105].

The degree of functional coupling during rest was predictive of neural engagement during the new learning experience itself. Through rest-phase reactivation and hippocampal–neocortical interactions, existing memories may come to facilitate encoding during subsequent related episodes[104].

In the PBL schedule, free time is doubly necessary: to study and to consolidate memory. It is thought that the consolidation of memory benefits from sleep[106-109]. Reprocessing of newly acquired material within hippocampal and neocortical networks occurs during sleep and could be a basis for long-term memory consolidation[110-112].

Hippocampal neural ensembles have been shown to replay place cell firing sequences during sleep and quiet waking periods following learning[113], and blocking this replay prevents subsequent memory retrieval[114].

In the PBL method, the process of setting the propositions to explain the questions presented in the given problem depends on the destabilization and restabilization of memory in the course of retrieving[115], updating, and integrating a given memory with other memories. Systems memory consolidation is one mechanism by which sleep can support memory formation. The reactivation of learning-related neural activity during sleep can be observed in the hippocampus and many other regions involved in learning[115,116].

Effective active learning must be given by trial and error and depends on neurons from the basal ganglia and the activity of dopamine[51,117]. In PBL, during step #6, an example of this is when students search for answers by reading information over and over again, despite not always arriving at the correct answer; thus, they encounter "trial and error" at their own pace.

The self-studying and deep problem-analysis phase provide the possibility to acquire a more profound knowledge of theories at the root of the problem1. Information is collected from the literature specified by the tutors and also from other sources. PBL allows students to find their own resources, thus experiencing independent learning. It will enable the integration and abstraction of sensory information[58].

This phase should provide answers to the questions posed. In this sense, number three of Figure 3 must be considered. Neurons from parietal areas interact with the neurons on the frontal lobes during problem-solving, evaluation, and hypothesis testing[118]. According to Schmidt et al[119], PBL is compatible with the human cognitive architecture.

The steps of PBL prior to self-study (1st to 5th steps), mainly in the brainstorming step, were devoted to activating the previous knowledge step and incorporating it into the new route of learning. Now (step #6), the students integrate new information provided by the discussion among their colleagues with their own recalled information, thus acquiring cognitive retention and learning generation[118]. However, students' knowledge about specific issues to solve the problem under discussion is incomplete yet. They have to perceive gaps in knowledge to establish ways to overcome them. According to Chi et

al.[78, 120], errors are necessary for learning to apply new knowledge. To successfully complete the last part of PBL (next step #7), students usually have one week to acquire sufficient knowledge to solve the problem. It is expected the students will elaborate and integrate new information due to previous learning and self-study.

Report back at the next tutorial to produce a comprehensive explanation of the phenomena and reapply newly acquired information to the problem (step #7).

The neuronal activity at this step of PBL should comprehend the neurons from the anterior cingulate (Brodmann area 32 - BA32)[58], concluding the links consecutively fulfilled by the learning. The anterior cingulate is implicated in response selection and inhibition of alternative responses once the best solution is determined in the previous stage[58].

The brainstorming process developed during step#3 and the present discussion highlights the importance of the collaborative[83] approach in PBL. It leads to greater creativity[79,121] and greater output than each group member could generate on his own[122].

Highly specific learning-induced plasticity in the primary auditory cortex (A1)[123] has been related to cortical metabolism. The cognitive functions of A1 go beyond pure stimulus features since its role also includes the analysis and storage of the behavioral significance of those features. The developing facilitated discrimination of various stimuli features perceptual learning, complex tasks, and rapid 'online' adjustments to maximize attentive capture of stimuli elements.

The neuromodulator acetylcholine (ACh) is particularly important among the mechanisms and effectors, acting on loci of active plasticity[124,125].

During this step, students share the results of self-study to achieve the learning goals[60]. Considering the stimulus of the students' intrinsic interest, this final step combines individual and collaborative skills[126-127].

Collaborative skills are particularly important in PBL[66, 89, 96, 128, 129]. however, implicit memory bias may arise when systematizing the learning. The hippocampus is involved in the cognitive processes that modify or bias memory[130]. Important research highlights that students are not always in the best position to judge which aspects of educational curricula are evidence-based[131]. If the students are not confident and not fluent with the new concepts involved in the given learning goals, they tend to be influenced more by wrong concepts provided by others during social exposure, leading to wrong learning structuration[130]. We reaffirm the responsibility[132] of the tutors[71, 133], and their role is now highlighted. Hippocampal-amygdala crosstalk is required to bring about implicit change in explicit memory[134]. A proper intervention must be taken to boost the functional connectivity between the hippocampus and the striatum, a brain area implicated in reward. The expertise of the tutors must be evidenced[135]. They are trained to probe students regarding the subject under discussion and stimulate critical assessment[136] of peer contributions to learning to help avoid memory bias. Memory efficiency is augmented by congruency-dependent interactions between the medial temporal lobe and the ventromedial prefrontal cortex[137]. Performance related to prior knowledge and item recognition is associated with increased intersubject synchronization of activity in the ventromedial prefrontal cortex and decreased hippocampal-ventromedial prefrontal cortex functional connectivity during encoding[137].

Long-lasting memory, but not temporary, false memory, was predicted by enhanced amygdala activity and hippocampal-amygdala functional connectivity during exposure to the social influence[130, 138]. The largely unconscious hippocampal-amygdala crosstalk was required to bring about implicit change in explicit memory[130] this change in memory is ultimately meaningful throughout all seven steps in PBL, as discussed earlier[139].

CONCLUSION

There is a well-documented science that underlies the neurocircuitry in each step of the student's learning process. Based upon the literature, we emphasized the importance of following the gradual development of PBL to construct neuro connections during the learning process. The current work described the neurophysiology in PBL based upon several aspects, such as the students' feeling of gratification by learning through problem-based methods.

PBL supports long-term memory retention and restructuring of thinking within its seven steps, thus generating knowledge supporting spiral learning.

There is substantial evidence that the hippocampus and neocortex are integral components in memory and information acquisition. Indeed, the hippocampus triggers the neocortex's activation connections, which may be crucial to strength learning during the PBL processes. Hence, further exploration of the neural pathways related to PBL proposed in this review represents a field of investigation to enrich the comprehension of active learning methods founded upon neuroscience.

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Note: Partial information was presented at a conference:
https://www.amee.org/getattachment/Conferences/AMEE-Past-Conferences/AMEE-2016/1-AMEE-2016-Abstract-Book-FULL-BOOK-UPDATED-Online-POST-CONFERENCE.pdf

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