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Unpacking and validating the 'Cell-Cell Communication' Core Concept of Physiology by an Australian team.

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ABSTRACT

An Australia-wide consensus was reached on seven core concepts of physiology, one of which was '*cell-cell communication*'. Three physiology educators from a 'core concepts' Delphi Task force, unpacked this core concept into seven different themes and sixty sub-themes. *Cell-cell communication*, previously 'unpacked' and validated, was modified for an Australian audience to include emerging knowledge and adapted to increase student accessibility. The unpacked hierarchical framework for this core concept was rated by twenty-four physiology educators from separate Australian Universities, using a five-point scale for level of importance for student understanding (ranging from 1=Essential to 5=Not Important) and level of difficulty (ranging from 1=Very Difficult to 5=Not Difficult). Data was analysed using the Kruskal-Wallis test with Dunn's multiple comparison test. The seven themes were rated within a narrow range of importance (1.13-2.4), with ratings of 'essential' or 'important,' and statistically significant differences between the themes ($P<0.0001$, n=7). The variance for the difficulty rating was higher than for importance, ranging from 2.15 ('Difficult') to 3.45 (between 'Moderately Difficult' and 'Slightly Difficult'). Qualitatively, it was suggested that some sub-themes were similar and that these could be grouped. However, all themes and sub-themes were ranked as 'important', validating this framework. Once finalised and adopted across Australian universities, the unpacked core concept for *cell-cell communication* will enable the generation of tools and resources for physiology educators and improvements in consistency across curricula.

Key words: cell-cell communication, core concepts, learning framework, curriculum, undergraduate education

New and noteworthy: Seven core concepts, including *cell-cell communication*, were identified by an Australian Delphi Task force of physiology educators. The previously

61 'unpacked' concept was adapted for Australian educators and students to develop a
62 framework with 7 themes and 67 sub-themes. The framework was successfully validated by
63 the original Delphi panel of educators and will provide a valuable resource for teaching and
64 learning in Australian Universities.
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66
67 **INTRODUCTION**
68 The use of core concepts or 'big ideas' enables the teaching of an overcrowded
69 curriculum, with a large and growing volume of detailed content, to shift towards a deeper
70 understanding of overarching core concepts (1, 6). Core concepts have been developed in a
71 range of fields, including Physiology (1, 6). In order to support educator and student
72 understanding, the core concepts are 'unpacked' to provide a framework or hierarchical map
73 of smaller themes and sub-themes (or descriptors), required for understanding of the larger
74 concept (1, 2). The frameworks underlying the Physiology core concepts facilitate the
75 implementation of core concepts into the curriculum, leading to a reduction in content and
76 improving teaching and student learning (1,6). There is global and growing interest from the
77 higher education sector for the core concepts in Physiology, with a proliferation of research
78 papers on this topic in *Advances in Physiology Education* (5-27A). Many of these papers
79 describe how the core concepts can be practically used in teaching (19) but there is also
80 evidence that the use of the core concepts enhances student learning (17).

81 Fifteen core concepts in undergraduate physiology were identified and developed by a
82 group of U.S. and international faculty (1) and a number of these concepts have been
83 unpacked (1-5). A recent study found poor correlation between these 15 core concepts of
84 physiology (2) and the Learning Outcomes of units (subjects) comprising undergraduate
85 physiology curricula across Australian universities (7). This suggested that there might be
86 differences in physiology curricula between the Australian, Northern American and European

higher education systems or that Australian Physiology educators were not aware of the original 15 core concepts (7, 8). This led a Task force of experienced, or senior, physiology educators from 25 Australian universities to revisit the 15 core concepts (8). The Task force utilised a Delphi approach (i.e. with a panel of expert physiology educators) to reach agreement upon a set of seven core concepts (and their descriptors): *Cell Membrane, Cell-cell Communication, Movement of Substances, Structure and Function, Homeostasis, Integration and Physiological Adaptation*. Only one of these concepts (*Physiological Adaptation*) was not adapted from the original 15 core concepts developed and published by Michael and colleagues (1. 9, 10). The other core concepts excluded from the final seven, whilst considered important, were thought to be better aligned with other non-physiology biomedical disciplines (8). Unpacking teams of three physiology educators, selected from the 25-member Task force, focused on unpacking each of the seven core concepts.

This present study focussed on the unpacking of the physiology concept of *Cell-cell communication* (2). Cells communicate with each other by sending and receiving signals. Cell-cell communication encompasses an expansive, multidisciplinary and rapidly growing field. The *Cell-cell communication* core concept, previously unpacked and validated by Michael *et al*. (1, 2), was expanded and modified to include themes and sub-themes reflecting the priorities and experiences of physiology educators at Australian Universities. Although these themes reflect parochial priorities of Australian Physiology educators, it remains axiomatic that these core concepts remain universal in application. Before we embarked on the unpacking of the *Cell-cell communication* core concept, there were differences in the overarching themes. These differences in themes necessarily resulted in variation in the sub-themes and unpacking. For example, we have introduced discussion of electrochemical signalling between cells (e.g. gap junctions in cardiac smooth muscle), and the chemical properties of chemical signalling molecules (lipophilic or hydrophilic) as important high level

ideas that can be applied generally to understand specific examples and learning outcomes. It was thus not surprising that the recent text analysis of Australian undergraduate Physiology Learning Outcomes, found particularly poor alignment with the *Cell-cell communication* concept (7). This supports a need to review and refine the *Cell-cell communication* core concept theme and sub-theme statements. By better defining and unpacking the core concepts and gaining the endorsement of Australian educators (27), this will facilitate their inclusion within Australian undergraduate physiology programs and provide a tool for educators to do so with consistency across these programs.

As this present study is specific to undergraduate physiology curricula for the Australian higher education context, in particular Physiology taught as a major (or a series of subjects/units/courses) with a Bachelor of Science or Biomedical Science degree program, it is important to understand how Australian Physiology curricula are determined. In Australia, the Tertiary Education Quality and Standards Agency (https://www.teqsa.gov.au/) accredits all programs of study, with oversight of the program learning outcomes to ensure that they are at the appropriate level for the study program (28). However, each university controls the learning outcomes at the level of Physiology subjects and this can lead to variability in Physiology learning outcomes.

This study evaluated the existing *Cell-Cell Communication* concept descriptors and refined these with the intended purpose of aligning learning outcomes at Australian tertiary institutions with the revised Core Concepts as unpacked by Australian physiology educators (27). The aim was to synthesize a framework that will assist Australian educators to teach this concept at a level easily understood by undergraduates and in the context to their program of study.

METHOD

The protocols for validating the unpacking of this core concept was adapted from Michael *et al*. (2). An Australian Task force performed a Delphi study to identify core concepts in physiology, which included *Cell-cell communication* (8). In the current study, the 'unpacked' *Cell-cell communication* conceptual framework by Michael *et al*., (1, 2) was modified by an 'unpacking team' of three educators (LC, JC and JR) from different Australian universities. With facilitation by MT, the team met virtually by Zoom to reach a consensus regarding the previously unpacked themes and sub-themes. Additional sub-themes were included by the team, which aimed to increase the accessibility of the terminology for an undergraduate student audience at all levels. The adapted framework included newer and emerging ideas in physiology compared to previous iterations (2). As described by Michael *et al*. (2), the term 'cell-cell communication' was limited in scope to 'communication at the level of the cell' and the team limited the unpacking to the field of 'human physiology'.

Task force and survey participants

The unpacked themes and sub-themes were entered into a Qualtrics survey and a link sent to the 25 physiology educators from the Task force which completed the Delphi protocol (see ref 8). Each participant works at a different Australian University, with all Australian States and the Australian Capital Territory represented. In Australia, Universities undertake both higher education teaching and research. Members of the Task force had a mean 16.42 (SD 7.17) years of experience teaching physiology at an undergraduate level. All survey respondents were experienced in aspects of physiology curriculum design, including the development of learning objectives, mapping course content and assessments to these learning objectives and the consideration of different modes of delivery (e.g. online, in person laboratories or tutorials)

Survey

Survey respondents were asked to rate the themes and sub-themes on a five point scale for level of importance for students to understand (1=Essential, 2=Important, 3=Moderately Important, 4=Slightly Important and 5=Not Important) and perceived level of difficulty for students (1=Very Difficult, 2= Difficult, 3=Moderately Difficult, 4=Slightly Difficult and 5=Not Difficult), based on the educators' experience (see 27). Respondents were asked for qualitative feedback regarding any changes that they would recommend for accuracy, readability, importance and difficulty as previously described by Tangalakis et al (8; See also 27).

Statistical Analyses

The mean and standard deviation were determined for each item for level of importance and level of difficulty. Survey responses were analysed using non-parametric Kruskal-Wallis tests and Dunn's multiple comparison test to compare themes and sub-themes. $P<0.05$ was considered statistically significant.

RESULTS

Survey respondents: Members of the initial Delphi Task force (n = 25), each from a different Australian University were surveyed, with a response rate of n = 24. Some respondents did not rank all sub-themes, however.

Survey results:

The 'unpacked' core concept for *Cell-cell communication* was adapted to produce a hierarchical conceptual framework with seven themes and 60 sub-themes and rated for respondents' perceptions of the level of importance and the level of difficulty (Table 1). The importance of each theme was rated on a five-point scale with the expert educators considering these themes to be 'essential' (rating of 1), 'important' (ratings of 2-4) or 'not

important' (rating of 5) for students to understand (Figure 1). The seven themes received perceived ratings for importance between 1.13 - 2.17 (1.58 ± 0.39, n=7) indicating that they were considered 'essential' or 'important' for physiology students to understand (Table 1). There was a statistically significant difference in the rating for importance between the themes ($P< 0.0001$, Kruskal-Wallis), with the highest-rated of the seven themes being Theme 1: Cell to cell communication occurs through electrochemical and chemical signaling' (1.13 ± 0.45, n= 24, Table 1) with a mean rating of 'essential'. This theme was rated statistically significantly more important than a number of other themes (Theme 3, $P = 0.0085$; Theme 6, $P = 0.0002$ and Theme 7, $P = 0.018$, Kruskal-Wallis test, Dunn's multiple comparison test, Table 1). Theme 4 was also rated statistically significantly more important than Theme 7 ($P = 0.0039$, n=7, Table 1).

The 60 sub-themes were rated for importance from 1.21-2.96, indicating that they were all considered to be at least 'moderately important' for students to understand (Table 1). Statistically significant differences in importance ratings were observed between the different themes and sub-themes ($P<0.0001$, n = 67; Table 1). A number of newer or emerging ideas in physiology that had not been described in the original unpacking of this core concept by Michael (1,9), were introduced. For example, traditionally it has been taught that hydrophobic, lipophilic hormones and molecules signal through intracellular, nuclear receptors, while hydrophilic messengers, which cannot pass through the lipid bilayer of the cell membrane signal through extracellular receptors (30, 34, 36). Some of these concepts rated lower than other sub-themes, with 'moderately important' ratings. This includes the sub-theme describing juxtacrine signaling '*1.1.6 Local communication can be contact dependent*' (2.16 ± 1.23, n=24, Table 1) which was ranked statistically significantly lower than its overarching theme (Theme 1, $P<0.001$, n=67). Sub-themes describing the role of exosomes in cell-cell communication (Sub-themes 1.15, 2.67) were rated between

213 'important' and 'moderately important' (Table 1), but were statistically significantly less
214 important than the higher-level theme 1 (P<0.0001, n=67). Similarly, the sub-theme
215 describing gases and eicosanoids as signaling molecules (Sub-theme 2.2.5, Table 1), was
216 ranked lower in importance than other sub-themes (2.74 ± 0.86, n=23) and statistically
217 significantly less important than Theme 2 (P<0.0001).

218 Qualitative comments about suggested changes (additions, deletions, corrections) for
219 themes and sub-themes for the cell-cell communication concept were provided by 17 of the
220 survey respondents. These suggestions, mainly about refining the wording of themes and sub-
221 themes to improve their clarity or accuracy, were considered by the unpacking team.
222 Although all themes and sub-themes were rated as at least 'moderately important', some
223 repetition was noted. For example, it was suggested by several respondents that sub-theme
224 4.3, stating that the hydrophobic or hydrophilic nature of a messenger can influence the
225 location of its receptor in or on a target cell, was unpacked into too many sub-themes. A
226 number of respondents noted that clarification was required for sub-theme 6.1 (n=4),
227 'messenger release must be ceased' and theme 7, regarding electrical communication via gap
228 junctions, could be omitted, as this concept is covered by theme 1 (n =3). Further refinement
229 of the 'unpacked' concept is required based on the feedback from the Task force.

230 The perceived level of difficulty for students to understand (the theme or sub-theme) was
231 rated by the expert educators from 'very difficult' [1] to 'not difficult' [5], with ratings for
232 seven themes between 3.04 - 3.78 (3.44 ± 0.26, n=7), or in the range from 'moderately
233 difficult' [3] to 'slightly difficult' [4] (Figure 2, Table 2). There were no statistically
234 significant differences between the themes. The level of difficulty of the sub-themes ranked
235 more broadly than the themes, ranging from 2.71 ('moderately difficult') to 4.18 ('slightly
236 difficult') (Figure 2, Table 2) with statistically significant differences being identified

between the total themes and sub-themes ($P<0.0001$, n=67). Sub-theme 4.2, 'A cell can only respond to a messenger for which it has receptors,' was rated 'slightly difficult,' was statistically significantly less difficult than a number of other sub-themes (Table 2).

DISCUSSION

Cell-cell communication was endorsed as a core concept in physiology by an Australian Task force using a Delphi panel method (8). This core concept was unpacked by a subgroup of the Task force ('unpacking team') and validated by the Task force. Originally 'unpacked' and validated as a core concept by Michael *et al*., (2), the published framework was used as a basis for developing a modified hierarchical framework suitable for Australian educators and undergraduate students. The modified framework was rated by members of the Task force using five-point scales for the level of importance for students to understand and for the level of difficulty for the students in order to validate the 'unpacking'.

All themes and sub-themes in *Cell-cell communication* were determined to be either 'essential', 'important' or 'moderately important' for undergraduate students to understand. Importance was largely rated higher for the overarching themes than the sub-themes. This is expected, as the framework is by definition hierarchical, with sub-themes being less important if they were lower in the hierarchy, as previously reported (2, 3). The framework consists of seven themes and 60 sub-themes, with up to four hierarchical levels. While some rationalisation of the number of sub-themes is desirable to reduce repetition, the number of items is not surprising given the broad scope of the core concept. There were significant differences in the level of importance between the themes or sub-themes. The meaningfulness of these observations remains to be determined. One possible explanation might be the individual teaching context of the educator, with some educators teaching Physiology as a

scientific discipline, where mechanism and scientific reasoning are a priority, and other educators teaching in the allied health education context, where the emphasis is on understanding human physiology in the context of health and disease. This remains to be explored in future research.

Cell-cell communication is a highly complex and constantly expanding field. It exemplifies the multidisciplinary nature of physiology and its significant overlap with disciplines including cell and molecular biology (2). It also illustrates its integrative nature, from the level of the molecule to the cellular and organismal level (2). *Cell-cell communication* is an important concept for numerous areas of physiology, including the nervous and endocrine systems, the cardiovascular, respiratory, renal and gastrointestinal systems (11) and integrated and environmental physiology. Core concepts are particularly important for this field as they enable educators to focus on key areas of knowledge that students need to acquire in light of an exponential rate of discovery (29). Furthermore, as new discoveries emerge, some long held 'general rules' and assumptions in this field can prove incorrect or inaccurate.

We maintained a relatively narrow definition of *Cell-cell communication* for the purpose of developing this framework, as described by Michael *et al*., (2). Silverthorn's (30) definition of cell-to-cell communication includes 'the use of chemical and electrical signaling to coordinate function and maintain homeostasis' (30). Long distance communication also involves action potentials, electrical signals in neurones (30), a concept not unpacked in detail here. The addition of a theme or concept to include the complex and important topic of action potentials could be considered in future iterations.

Some sub-themes in physiology that were added to the conceptual framework for *Cell-cell communication* were ranked lower than other sub-themes. Although accepted in the literature,

these sub-themes have not yet been widely integrated into all physiology text books. This includes the role of exosomes and extracellular vesicles in cell-cell communication (31-33), which is briefly introduced by Boulpaep (34). Signaling molecules, including gases, and signaling mechanisms such as contact-dependent signaling through cell adhesion molecules (CAMs) have been described by Silverthorn (30) and Boulpaep (34). Eicosanoids, signaling molecules with key roles in a range of physiological processes (35), have also been described in some physiology texts (30, 36). The fact that these ideas are not yet described in all standard physiology textbooks could influence the lower rating of these sub-themes in terms of importance.

There are some stark differences between the descriptors (themes/sub-themes) for the *Cell-Cell Communication* core concept proposed here and the descriptors proposed by Michaels et al (1-3, see Table 3). What is immediately obvious when you compare the concept descriptors/themes is that we have included discussion about electrical signalling between cells (via gap junctions) which is absent from the earlier Michael's themes. Physiologically, communication via gap junctions is crucial for understanding physiology of both cardiac and smooth muscle (30, 34. 36). While action potentials are intracellular signalling, transmission of depolarizing signals that lead to synchronised muscle contraction are due to communication through electrically coupled cells. We have also combined both Michael's descriptors for the core concept ('CC4' and 'CC5') into one Theme (theme 5). Thus, although both groups end up with seven themes or 'CC's, there are subtle differences in the emphasis between the two. A key difference between the two frameworks is that the new proposal makes a virtue of understanding the chemical properties of the signalling molecules, and the impact this has on both the molecule behaviour and how it interacts with its receptor.

A number of newer or emerging ideas were incorporated into this unpacking of the cell-cell communication core concept. For example, it is now well established that hydrophobic hormones and messengers can rapidly signal through transmembrane receptors (30, 34, 36), and not only through intracellular, nuclear receptors. Exosomes and extracellular vesicles are emerging as important communication vehicles (31-33) and messenger molecules are now known to be more diverse, including gases (38, 39), lipids, RNA and DNA (40). Although the concept of juxtacrine signaling has been recognised for some time (41),

The aim of identifying core concepts and unpacking these 'big ideas' into their underlying important constituents is to provide guidance and to generate an important tool for teaching and learning (4). Although one of the aims of adapting the core concept of *Cell-cell communication* was to improve the accessibility of the themes and sub-themes for undergraduate students, this framework requires testing with a student audience. Qualitative comments indicated that some sub-themes were not as easy to understand as others and further modifications are therefore required.

Unpacked core concepts can be used by educators to structure and design curriculum, including new courses, using a backward design approach (6, 18). This framework will facilitate the generation of numerous resources to enable the implementation of the core concept and to enhance student learning. This can include concept inventories, learning objectives, formative and summative assessments, and the design of active learning approaches (6, 9, 13). The adoption of core concepts in Australian Universities will lead to increased consistency in the curriculum and provide an additional and powerful tool for students and educators.

The core concepts as proposed by Michael and colleagues (1, 6, 9. 10) have been transformative of how physiology educators approach their teaching design. The context of

this paper should not be seen as an attempt to replace the original core concept, but rather to refine them to reflect local priorities. Ultimately, physiology core concepts should be universally applicable, even if undergoing constant refinement.

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453 **Table 1: Level of importance for students to understand themes and sub-themes rated**
454 **by Task force members.**

Themes and sub-themes	Level of Importance		
	Mean	**SD**	**n**
1. Cell to cell communication occurs through electrochemical and chemical signaling and can be local or long distance.	1.13	0.45	24
1.1 Local communication occurs through electrochemical and chemical signaling.	1.29	0.55	24
1.1.1 Gap junctions allow direct electrochemical communication between adjacent cells.	1.92	1.02	24
1.1.2 Gap junctions allow movement of molecules between adjacent cells.	2.78	1.09	23
1.1.3 Autocrine signaling occurs when a chemical messenger acts on the cell that releases the messenger.	2.04	0.75	24
1.1.4 Paracrine signaling occurs where a chemical messenger diffuses to the site to act on adjacent cells.	1.83	0.76	24
1.1.5 Signaling through extracellular vesicles (including exosomes) allows local cell to cell communication, and transport messengers including proteins, non-coding RNAs, DNA and lipid signals.	2.67	1.09	24
1.1.6 Local communication can be contact dependent. Cell surface cell adhesion molecules (CAMs) allow bidirectional signaling across the cell membrane of two cells when in direct contact.	2.96	1.23	24
1.2 Long-distance signaling occurs through chemical signaling in the nervous system and through chemical signaling (hormones) in the endocrine system.	1.21	0.42	24
1.2.1 The endocrine system secretes hormones (chemical messengers) into the bloodstream which can exert long lasting effects.	1.21	0.42	24
1.2.2 The nervous system releases chemical signals as neurotransmitters and neuromodulators at the synapse.	1.29	0.46	24
1.2.3 Exosomes are released from most cell types, and transport messengers (including RNA, DNA, protein and metabolites) over long distances.	2.83	1.31	24

2. A cell synthesises and releases a chemical messenger.	1.38	0.58	24
2.1 Messenger molecules can be proteins (or peptides), steroids, lipids, amines, amino acids, DNA, RNA or gases.	1.63	0.77	24
2.2 A cell synthesises a messenger molecule and either stores the messenger in vesicles or it escapes by diffusion.	1.96	0.96	24
2.2.1 Peptides/proteins are synthesised in the cell and stored in secretory vesicles prior to release.	2.04	0.83	23
2.2.2 Steroid hormones are synthesised as required and diffuse from the cell.	2.26	0.81	23
2.2.3 Catecholamines are synthesized and stored in secretory vesicles.	2.57	0.95	23
2.2.4 Some hormones are produced and stored in an inactive form and cleavage leads to the active product (e.g. thyroid hormones and proinsulin/insulin).	2.54	1.02	24
2.2.5 Gases and eicosanoids are synthesised as required and diffuse across the cell membrane.	2.74	0.86	23
2.3 The rate of release of a chemical messenger from a cell is determined by the “sum” of the stimuli promoting and inhibiting that release.	2.25	0.68	24
2.4 Chemical signaling molecules can have biological effects even at low extracellular concentrations.	2.21	0.83	24
2.5 Chemical messengers that are stored prior to release can be secreted from the cell via exocytosis, or through the release of vesicles such as exosomes.	2.43	0.90	23
2.6 Cells that release messengers can be anywhere in the body.	1.87	0.69	23
3. The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.	1.79*	0.78	24
3.1 The solubility of the molecule can influence how it is transported to its target cells.	2.17	1.09	24
3.1.1 Hydrophobic chemical messengers must travel with other carrier molecules i.e., binding proteins or plasma proteins.	2.13	0.85	24
3.1.2 Hydrophilic chemical messengers can travel dissolved in aqueous solution, attached to a binding protein, or transported within an exosome.	2.17	0.92	24
3.2 Only the messenger in solution which is free to diffuse is	2.25	0.90	24

biologically active.			
3.2.1 A chemical messenger bound to a binding protein in solution is biologically unavailable.	2.50	0.83	24
3.3 The extracellular fluid concentration of a messenger molecule depends on the balance between the production, release and elimination of messenger molecules.	2.38	0.77	24
4. The messenger must bind to a receptor protein in or on its target cell to produce a response.	1.21	0.42	24
4.1 Each messenger molecule binds with a certain affinity to a specific receptor molecule.	1.92	0.93	24
4.1.1 Binding of a messenger to its receptor is a probabilistic event.	2.75	0.99	24
4.2 A cell can only respond to a messenger for which it has receptors.	1.33	0.48	24
4.3 The solubility/hydrophobicity of the messenger can influence the location of its receptor protein in/on the target cell.	2.04	0.86	24
4.3.1 Water-soluble (hydrophilic) primary messengers cannot pass through the cell membrane.	1.78	0.74	23
4.3.2 Water-soluble (hydrophilic) primary messengers signal through receptors on the target cell membrane (extracellular receptors).	1.70	0.64	23
4.3.3 Lipid soluble (hydrophobic) messengers can pass through the cell membrane.	1.83	0.83	23
4.3.4 Lipid soluble (hydrophobic) messengers can signal through either intracellular (cytoplasmic or nuclear) or extracellular receptors.	2.13	0.76	23
4.3.5 Lipid soluble messengers that bind with intracellular receptors can interact with DNA to mediate genomic effects.	2.17	0.94	23
4.3.6 Lipid soluble messengers that bind with extracellular receptors can mediate non-genomic effects.	2.65	1.07	23
4.4 The number of receptors for a particular messenger is variable.	2.46	0.83	24
4.5 There can be more than one type of receptor for the same messenger on different target cells, including different isoforms of the same receptor.	2.33	0.92	24
4.6 It is the receptor that determines the cellular response.	1.52	0.73	23

4.6.1 The same chemical signaling molecule can elicit a range of cellular responses based on the receptor subtypes it binds.	2.00	0.83	24
4.6.2 Cells have a large variety of different receptors, thus enabling them to respond to a large number of different messengers.	1.79	0.59	24
5. Binding of the messenger molecule to its receptor gives rise to signal transduction.	1.46	0.66	24
5.1 A single messenger molecule bound to its receptor can lead to the activation of signaling cascades to amplify the signal.	1.96	0.81	24
5.1.1 Because the target cell response is a multistep process and amplification occurs at each step, a single molecule can activate or alter many more molecules; the more steps in the intracellular signaling process, the greater the amplification can be.	2.54	1.02	24
5.1.2 Because the target cell response is a multistep process, there are many points at which different inputs (other messengers) can modify the response. This is referred to as integration.	2.50	0.93	24
5.2 There are a number of basic mechanisms for signal transduction.	2.05	0.84	22
5.2.1 Binding of a messenger molecule to an extracellular receptor can lead to signaling through a range of processes including the activation of enzymes, G proteins or opening of ion channels.	1.83	0.82	24
5.2.2 Ion flux can activate signal transduction pathways and alter excitability	2.09	1.04	23
5.2.3 Binding of a messenger molecule to a receptor can regulate gene expression.	2.04	0.64	23
5.2.4 The speed of the response to signaling pathways varies according to the signaling pathway.	2.75	1.19	24
5.2.4.1 Ion channels are the fastest response mechanism	2.35	0.98	23
5.2.4.2 The signaling response for extracellular receptors and second messenger systems are rapid as second messenger molecules are already present in the cell and can be rapidly inactivated.	2.48	0.95	23
5.2.4.3 The genomic signaling effects are slower, as transcription and translation of new molecules is required.	2.39	0.72	23

6. Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.	2.17*$	1.09	24
6.1 Messenger release must be ceased.	2.36	1.09	22
6.2 The messenger signal can be terminated when the molecule is removed, either through diffusion (concentration becomes too low) or via chemical breakdown by enzymes or via specific transport or uptake into compartments away from the receptor.	2.17	0.98	23
6.3 The messenger molecule must dissociate from the receptor or the receptor- messenger complex, can be internalized by endocytosis and digested in the cell and the complex will cease to generate a signal.	2.48	1.08	23
6.4 Receptors can be made unavailable through internalisation, down regulation or through pharmacological antagonism.	2.65	0.88	23
7. Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.	1.91*	1.15	22
7.1 When electrically excited, current (ions) can flow from the excited cell to neighbouring cells via the gap junctions.	2.05	1.00	22
7.2 These currents then electrically excite the second cell synchronising depolarisation across a whole tissue.	2.09	0.87	22

Themes and sub-themes were rated on a 5-point scale for level of importance for the students to understand (1=Essential, 2=Important, 3=Moderately Important, 4=Slightly Important and 5=Not Important). SD = standard deviation. n = number of respondents. *Themes rated statistically significantly less important than theme 1 ($P < 0.05$). $^{\$}$Theme rated statistically significantly less important than theme 4 (P=0.004). Kruskal-Wallis test with Dunn's multiple comparison test.

462 **Table 2: Level of difficulty for students to understand themes and sub-themes, rated by**
463 **Task force members.**

	Level of Difficulty		
	Mean	SD	n
1. Cell to cell communication occurs through electrochemical and chemical signaling and can be local or long distance.	3.25	0.85	24
1.1 Local communication occurs through electrochemical and chemical signaling.	3.21	0.93	24
1.1.1 Gap junctions allow direct electrochemical communication between adjacent cells.	3.48	0.73	23
1.1.2 Gap junctions allow movement of molecules between adjacent cells.	3.36	0.95	22
1.1.3 Autocrine signaling occurs when a chemical messenger acts on the cell that releases the messenger.	3.67	0.87	24
1.1.4 Paracrine signaling occurs where a chemical messenger diffuses to the site to act on adjacent cells.	3.75	0.74	24
1.1.5 Signaling through extracellular vesicles (including exosomes) allow the local cell to cell communication, and transport messengers including proteins, non-coding RNAs, DNA and lipid signals.	2.71	0.86	24
1.1.6 Local communication can be contact dependent. Cell surface cell adhesion molecules (CAMs) allow bidirectional signaling across the cell membrane of two cells when in direct contact.	2.91	0.79	23
1.2 Long-distance signaling occurs through electrochemical signaling in the nervous system and through chemical signaling (hormones) in the endocrine system.	3.54	0.83	24
1.2.1 The endocrine system secretes hormones (chemical messengers) into the bloodstream which can exert long lasting effects.	3.71	0.81	24
1.2.2 The nervous system releases chemical signals as neurotransmitters and neuromodulators at the synapse.	3.50	0.78	24
1.2.3 Exosomes are released from most cell types, and transport messengers (including RNA, DNA, protein and metabolites) over long distances.	3.00	0.95	23

2. A cell synthesizes and releases a chemical messenger.	3.75	0.90	24
2.1 Messenger molecules can be proteins (or peptides), steroids, lipids, amines, amino acids, DNA, RNA or gases.	3.50	0.98	24
2.2 A cell synthesizes a messenger molecule and either stores the messenger in vesicles or it escapes by diffusion.	3.57	0.84	23
2.2.1 Peptides/proteins are synthesized in the cell and stored in secretory vesicles prior to release.	3.70	0.88	23
2.2.2 Steroid hormones are synthesized as required and diffuse from the cell.	3.57	0.90	23
2.2.3 Catecholamines are synthesized and stored in secretory vesicles.	3.59	0.96	22
2.2.4 Some hormones are produced and stored in an inactive form and cleavage leads to the active product (e.g. thyroid hormones and proinsulin/insulin).	3.22	0.95	23
2.2.5 Gases and eicosanoids are synthesized as required and diffuse across the cell membrane.	3.41	0.80	24
2.3 The rate of release of a chemical messenger from a cell is determined by the “sum” of the stimuli promoting and inhibiting that release.	3.08	0.88	24
2.4 Chemical signaling molecules can have biological effects even at low extracellular concentrations.	3.65	1.03	23
2.5 Chemical messengers that are stored prior to release can be secreted from the cell via exocytosis, or through the release of vesicles such as exosomes.	3.32	0.72	22
2.6 Cells that release messengers can be anywhere in the body.	4.18	0.85	22
3. The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.	3.46	0.98	24
3.1 The solubility of the molecule can influence how it is transported to its target cells.	3.42	0.97	24
3.1.1 Hydrophobic chemical messengers must travel with other carrier molecules i.e. binding proteins or plasma proteins	3.33	0.96	24
3.1.2 Hydrophilic chemical messengers can travel dissolved in aqueous solution, attached to a binding protein, or transported within an exosome.	3.42	0.93	24
3.2 Only the messenger in solution and free to diffuse is	3.42	0.97	24

biologically active.			
3.2.1 A chemical messenger bound to a binding protein in solution is biologically unavailable.	3.42	0.88	24
3.3 The extracellular fluid concentration of a messenger molecule depends on the balance between the production, release and elimination of messenger molecules.	3.33	0.96	24
4. The messenger must bind to a receptor protein in or on its target cell to produce a response.	3.78	1.04	23
4.1 Each messenger molecule binds with a certain affinity to a specific receptor molecule.	3.09	0.79	23
4.1.1 Binding of a messenger to its receptor is a probabilistic event.	2.74	1.01	23
4.2 A cell can only respond to a messenger for which it has receptors.	4.13	0.92	23
4.3 The solubility/hydrophobicity of the messenger can influence the location of its receptor protein in/on the target cell.	3.61	0.89	23
4.3.1 Water-soluble (hydrophilic) primary messengers cannot pass through the cell membrane.	3.82	0.91	22
4.3.2 Water-soluble (hydrophilic) primary messengers signal through receptors on the target cell membrane (extracellular receptors).	3.77	0.92	22
4.3.3 Lipid soluble (hydrophobic) messengers can pass through the cell membrane.	3.82	0.85	22
4.3.4 Lipid soluble (hydrophobic) messengers can signal through either intracellular (cytoplasmic or nuclear) or extracellular receptors.	3.64	0.79	22
4.3.5 Lipid soluble messengers that bind with intracellular receptors can interact with DNA to mediate genomic effects.	3.18	0.91	22
4.3.6 Lipid soluble messengers that bind with extracellular receptors can mediate non-genomic effects.	3.18	0.80	22
4.4 The number of receptors for a particular messenger is variable.	3.74	1.05	23
4.5 There can be more than one type of receptor for the same messenger on different target cells, including different isoforms of the same receptor.	3.09	0.85	23
4.6 It is the receptor that determines the cellular response.	3.27	1.12	22

4.6.1 The same chemical signaling molecule can elicit a range of cellular responses based on the receptor subtypes it binds.	2.96	0.98	23
4.6.2 Cells have a large variety of different receptors, thus enabling them to respond to a large number of different messengers.	3.48	1.16	23
5. Binding of the messenger molecule to its receptor gives rise to signal transduction.	3.33	0.96	24
5.1 A single messenger molecule bound to its receptor can lead to the activation of signaling cascades to amplify the signal.	3.04	1.00	24
5.1.1 Because the target cell response is a multistep process and amplification occurs at each step, a single molecule can activate or alter many more molecules; the more steps in the intracellular signaling process, the greater the amplification can be.	3.00	1.00	23
5.1.2 Because the target cell response is a multistep process, there are many points at which different inputs (other messengers) can modify the response. This is referred to as integration.	2.70	0.82	23
5.2 There are a number of basic mechanisms for signal transduction.	3.23*	0.97	22
5.2.1 Binding of a messenger molecule to an extracellular receptor can lead to signaling through a range of processes including the activation of enzymes, G proteins or opening of ion channels.	2.88	0.90	24
5.2.2 Ion flux can activate signal transduction pathways and alter excitability	2.91*	0.87	22
5.2.3 Binding of a messenger molecule to a receptor can regulate gene expression.	3.00	0.74	23
5.2.4 The speed of the response to signaling pathways varies according to the signaling pathway.	3.59	0.85	22
5.2.4.1 Ion channels are the fastest response mechanism	3.74	1.05	23
5.2.4.2 The signaling response for extracellular receptors and second messenger systems are rapid as second messenger molecules are already present in the cell and can be rapidly inactivated.	3.00	0.82	22
5.2.4.3 The genomic signaling effects are slower, as transcription and translation of new molecules is required.	3.26	0.96	23

6. Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.	3.04	0.86	24
6.1 Messenger release must be ceased.	4.05	0.92	21
6.2 The messenger signal can be terminated when the molecule is removed, either through diffusion (concentration becomes too low) or via chemical breakdown by enzymes or via specific transport or uptake into compartments away from the receptor.	3.22	0.85	23
6.3 The messenger molecule must dissociate from the receptor or the receptor- messenger complex, can be internalized by endocytosis and digested in the cell and the complex will cease to generate a signal.	2.96	0.95	22
6.4 Receptors can be made unavailable through internalisation, down regulation or through pharmacological antagonism.	2.87*	0.87	23
7. Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.	3.48	0.98	21
7.1 When electrically excited, current (ions) can flow from the excited cell to neighbouring cells via the gap junctions.	3.33	0.97	21
7.2 These currents then electrically excite the second cell synchronising depolarisation across the whole tissue.	3.14	0.85	21

Level of difficulty for students (1=Very Difficult, 2=Difficult, 3=Moderately Difficult, 4=Slightly Difficult and 5=Not Difficult) was rated by Task force members. SD = standard deviation. n = number of respondents. * Theme or sub-theme statistically significantly more difficult than 4.2 *A cell can only respond to a messenger for which it has receptors*. ($P < 0.05$ Kruskal-Wallis test with Dunn's multiple comparison test).

Figure 1: Distribution of level of importance for students to understand ranked by members of the Task force for Themes from the cell-cell communication framework. (1=Essential, 2=Important, 3=Moderately Important, 4=Slightly Important and 5=Not Important).

Figure 2: Distribution of level of difficulty for students ranked by members of the Task force for Themes from the cell-cell communication framework. (1=Very Difficult, 2=Difficult, 3=Moderately Difficult, 4=Slightly Difficult and 5=Not Difficult)

TABLE 3: Comparison of major themes for the *Cell-Cell Communication* core concepts between Michael *et al* (1,2) and this current study.

Core Concept Descriptors (CC: Michaels) or Theme (Chopin)	Michael et al 2017	Chopin et al 2023
CC1 Theme 1	A cell synthesizes and releases a chemical messenger.	Cell to cell communication occurs through electrochemical and chemical signaling and can be local or long distance.
CC2 Theme 2	Transport of messenger molecules is determined by the chemical nature of the messenger.	A cell synthesises and releases a chemical messenger.
CC3 Theme 3	The messenger must bind to a receptor protein in or on its target cell to produce a response.	The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.
CC4 Theme 4	Binding of the messenger molecule to its receptor gives rise to signal transduction.	The messenger must bind to a receptor protein in or on its target cell to produce a response.
CC5 Theme 5	Binding of the messenger molecule to its receptor alters cell function.	Binding of the messenger molecule to its receptor gives rise to signal transduction.
CC6 Theme 6	Termination of a messenger signal is accomplished in several ways.	Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.
CC7 Theme 7	Some cells can communicate with neighboring cells electrically; they are electrically coupled.	Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.

Comparison of the CC themes between the Michael et al (1,2) and the outcomes of this study. Boxes with same shading (black or grey, with black or white text) indicated CC themes are common between Michael and Chopin. Unshaded boxes (white fill) indicate CC themes that are specific to the particular study. Four of the seven CC themes in each study are the same or similar, while three from each study are unaligned.

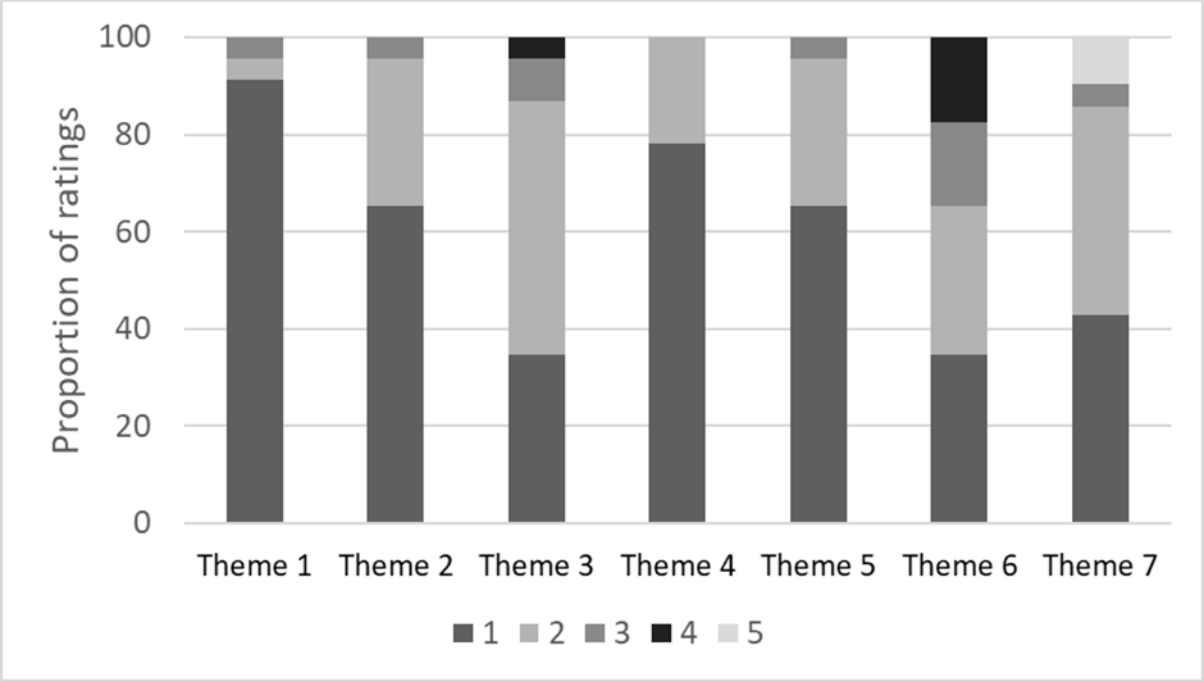

Figure 1: Distribution of level of importance for students to understand ranked by members of the Task force for Themes from the cell-cell communication framework. (1=Essential, 2=Important, 3=Moderately Important, 4=Slightly Important and 5=Not Important).

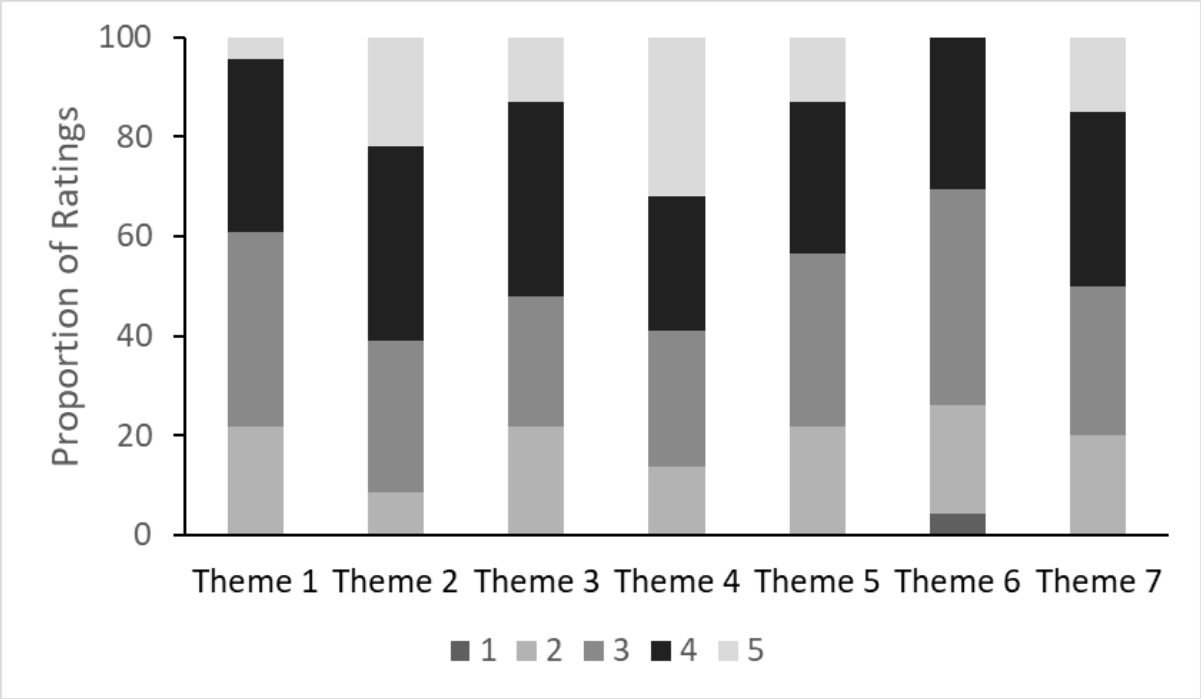

Figure 2: Distribution of level of difficulty for students ranked by members of the Task force for Themes from the cell-cell communication framework. (1=Very Difficult, 2=Difficult, 3=Moderately Difficult, 4=Slightly Difficult and 5=Not Difficult)

Table 1: Level of importance for students to understand themes and sub-themes rated by Task force members.

Themes and sub-themes	Level of Importance		
	Mean	**SD**	**n**
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1.1.3 Autocrine signaling occurs when a chemical messenger acts on the cell that releases the messenger.	2.04	0.75	24
1.1.4 Paracrine signaling occurs where a chemical messenger diffuses to the site to act on adjacent cells.	1.83	0.76	24
1.1.5 Signaling through extracellular vesicles (including exosomes) allows local cell to cell communication, and transport messengers including proteins, non-coding RNAs, DNA and lipid signals.	2.67	1.09	24
1.1.6 Local communication can be contact dependent. Cell surface cell adhesion molecules (CAMs) allow bidirectional signaling across the cell membrane of two cells when in direct contact.	2.96	1.23	24
1.2 Long-distance signaling occurs through chemical signaling in the nervous system and through chemical signaling (hormones) in the endocrine system.	1.21	0.42	24
1.2.1 The endocrine system secretes hormones (chemical messengers) into the bloodstream which can exert long lasting effects.	1.21	0.42	24
1.2.2 The nervous system releases chemical signals as neurotransmitters and neuromodulators at the synapse.	1.29	0.46	24
1.2.3 Exosomes are released from most cell types, and transport messengers (including RNA, DNA, protein and metabolites) over long distances.	2.83	1.31	24
2. A cell synthesises and releases a chemical messenger.	1.38	0.58	24

2.1 Messenger molecules can be proteins (or peptides), steroids, lipids, amines, amino acids, DNA, RNA or gases.	1.63	0.77	24
2.2 A cell synthesises a messenger molecule and either stores the messenger in vesicles or it escapes by diffusion.	1.96	0.96	24
2.2.1 Peptides/proteins are synthesised in the cell and stored in secretory vesicles prior to release.	2.04	0.83	23
2.2.2 Steroid hormones are synthesised as required and diffuse from the cell.	2.26	0.81	23
2.2.3 Catecholamines are synthesized and stored in secretory vesicles.	2.57	0.95	23
2.2.4 Some hormones are produced and stored in an inactive form and cleavage leads to the active product (e.g. thyroid hormones and proinsulin/insulin).	2.54	1.02	24
2.2.5 Gases and eicosanoids are synthesised as required and diffuse across the cell membrane.	2.74	0.86	23
2.3 The rate of release of a chemical messenger from a cell is determined by the “sum” of the stimuli promoting and inhibiting that release.	2.25	0.68	24
2.4 Chemical signaling molecules can have biological effects even at low extracellular concentrations.	2.21	0.83	24
2.5 Chemical messengers that are stored prior to release can be secreted from the cell via exocytosis, or through the release of vesicles such as exosomes.	2.43	0.90	23
2.6 Cells that release messengers can be anywhere in the body.	1.87	0.69	23
3. The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.	1.79*	0.78	24
3.1 The solubility of the molecule can influence how it is transported to its target cells.	2.17	1.09	24
3.1.1 Hydrophobic chemical messengers must travel with other carrier molecules i.e., binding proteins or plasma proteins.	2.13	0.85	24
3.1.2 Hydrophilic chemical messengers can travel dissolved in aqueous solution, attached to a binding protein, or transported within an exosome.	2.17	0.92	24
3.2 Only the messenger in solution which is free to diffuse is biologically active.	2.25	0.90	24
3.2.1 A chemical messenger bound to a binding protein in solution is biologically unavailable.	2.50	0.83	24

3.3 The extracellular fluid concentration of a messenger molecule depends on the balance between the production, release and elimination of messenger molecules.	2.38	0.77	24
4. The messenger must bind to a receptor protein in or on its target cell to produce a response.	1.21	0.42	24
4.1 Each messenger molecule binds with a certain affinity to a specific receptor molecule.	1.92	0.93	24
4.1.1 Binding of a messenger to its receptor is a probabilistic event.	2.75	0.99	24
4.2 A cell can only respond to a messenger for which it has receptors.	1.33	0.48	24
4.3 The solubility/hydrophobicity of the messenger can influence the location of its receptor protein in/on the target cell.	2.04	0.86	24
4.3.1 Water-soluble (hydrophilic) primary messengers cannot pass through the cell membrane.	1.78	0.74	23
4.3.2 Water-soluble (hydrophilic) primary messengers signal through receptors on the target cell membrane (extracellular receptors).	1.70	0.64	23
4.3.3 Lipid soluble (hydrophobic) messengers can pass through the cell membrane.	1.83	0.83	23
4.3.4 Lipid soluble (hydrophobic) messengers can signal through either intracellular (cytoplasmic or nuclear) or extracellular receptors.	2.13	0.76	23
4.3.5 Lipid soluble messengers that bind with intracellular receptors can interact with DNA to mediate genomic effects.	2.17	0.94	23
4.3.6 Lipid soluble messengers that bind with extracellular receptors can mediate non-genomic effects.	2.65	1.07	23
4.4 The number of receptors for a particular messenger is variable.	2.46	0.83	24
4.5 There can be more than one type of receptor for the same messenger on different target cells, including different isoforms of the same receptor.	2.33	0.92	24
4.6 It is the receptor that determines the cellular response.	1.52	0.73	23
4.6.1 The same chemical signaling molecule can elicit a range of cellular responses based on the receptor subtypes it binds.	2.00	0.83	24
4.6.2 Cells have a large variety of different receptors, thus enabling them to respond to a large number of different messengers.	1.79	0.59	24

5. Binding of the messenger molecule to its receptor gives rise to signal transduction.	1.46	0.66	24
5.1 A single messenger molecule bound to its receptor can lead to the activation of signaling cascades to amplify the signal.	1.96	0.81	24
5.1.1 Because the target cell response is a multistep process and amplification occurs at each step, a single molecule can activate or alter many more molecules; the more steps in the intracellular signaling process, the greater the amplification can be.	2.54	1.02	24
5.1.2 Because the target cell response is a multistep process, there are many points at which different inputs (other messengers) can modify the response. This is referred to as integration.	2.50	0.93	24
5.2 There are a number of basic mechanisms for signal transduction.	2.05	0.84	22
5.2.1 Binding of a messenger molecule to an extracellular receptor can lead to signaling through a range of processes including the activation of enzymes, G proteins or opening of ion channels.	1.83	0.82	24
5.2.2 Ion flux can activate signal transduction pathways and alter excitability	2.09	1.04	23
5.2.3 Binding of a messenger molecule to a receptor can regulate gene expression.	2.04	0.64	23
5.2.4 The speed of the response to signaling pathways varies according to the signaling pathway.	2.75	1.19	24
5.2.4.1 Ion channels are the fastest response mechanism	2.35	0.98	23
5.2.4.2 The signaling response for extracellular receptors and second messenger systems are rapid as second messenger molecules are already present in the cell and can be rapidly inactivated.	2.48	0.95	23
5.2.4.3 The genomic signaling effects are slower, as transcription and translation of new molecules is required.	2.39	0.72	23
6. Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.	2.17*$	1.09	24
6.1 Messenger release must be ceased.	2.36	1.09	22

6.2 The messenger signal can be terminated when the molecule is removed, either through diffusion (concentration becomes too low) or via chemical breakdown by enzymes or via specific transport or uptake into compartments away from the receptor.	2.17	0.98	23
6.3 The messenger molecule must dissociate from the receptor or the receptor- messenger complex, can be internalized by endocytosis and digested in the cell and the complex will cease to generate a signal.	2.48	1.08	23
6.4 Receptors can be made unavailable through internalisation, down regulation or through pharmacological antagonism.	2.65	0.88	23
7. Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.	1.91*	1.15	22
7.1 When electrically excited, current (ions) can flow from the excited cell to neighbouring cells via the gap junctions.	2.05	1.00	22
7.2 These currents then electrically excite the second cell synchronising depolarisation across a whole tissue.	2.09	0.87	22

Themes and sub-themes were rated on a 5-point scale for level of importance for the students to understand (1=Essential, 2=Important, 3=Moderately Important, 4=Slightly Important and 5=Not Important). SD = standard deviation. n = number of respondents. *Themes rated statistically significantly less important than theme 1 ($P < 0.05$). $^{\$}$Theme rated statistically significantly less important than theme 4 (P=0.004). Kruskal-Wallis test with Dunn's multiple comparison test.

Table 2: Level of difficulty for students to understand themes and sub-themes, rated by Task force members.

	Level of Difficulty		
	Mean	SD	n
1. Cell to cell communication occurs through electrochemical and chemical signaling and can be local or long distance.	3.25	0.85	24
1.1 Local communication occurs through electrochemical and chemical signaling.	3.21	0.93	24
1.1.1 Gap junctions allow direct electrochemical communication between adjacent cells.	3.48	0.73	23
1.1.2 Gap junctions allow movement of molecules between adjacent cells.	3.36	0.95	22
1.1.3 Autocrine signaling occurs when a chemical messenger acts on the cell that releases the messenger.	3.67	0.87	24
1.1.4 Paracrine signaling occurs where a chemical messenger diffuses to the site to act on adjacent cells.	3.75	0.74	24
1.1.5 Signaling through extracellular vesicles (including exosomes) allow the local cell to cell communication, and transport messengers including proteins, non-coding RNAs, DNA and lipid signals.	2.71	0.86	24
1.1.6 Local communication can be contact dependent. Cell surface cell adhesion molecules (CAMs) allow bidirectional signaling across the cell membrane of two cells when in direct contact.	2.91	0.79	23
1.2 Long-distance signaling occurs through electrochemical signaling in the nervous system and through chemical signaling (hormones) in the endocrine system.	3.54	0.83	24
1.2.1 The endocrine system secretes hormones (chemical messengers) into the bloodstream which can exert long lasting effects.	3.71	0.81	24
1.2.2 The nervous system releases chemical signals as neurotransmitters and neuromodulators at the synapse.	3.50	0.78	24
1.2.3 Exosomes are released from most cell types, and transport messengers (including RNA, DNA, protein and metabolites) over long distances.	3.00	0.95	23
2. A cell synthesizes and releases a chemical messenger.	3.75	0.90	24

2.1 Messenger molecules can be proteins (or peptides), steroids, lipids, amines, amino acids, DNA, RNA or gases.	3.50	0.98	24
2.2 A cell synthesizes a messenger molecule and either stores the messenger in vesicles or it escapes by diffusion.	3.57	0.84	23
2.2.1 Peptides/proteins are synthesized in the cell and stored in secretory vesicles prior to release.	3.70	0.88	23
2.2.2 Steroid hormones are synthesized as required and diffuse from the cell.	3.57	0.90	23
2.2.3 Catecholamines are synthesized and stored in secretory vesicles.	3.59	0.96	22
2.2.4 Some hormones are produced and stored in an inactive form and cleavage leads to the active product (e.g. thyroid hormones and proinsulin/insulin).	3.22	0.95	23
2.2.5 Gases and eicosanoids are synthesized as required and diffuse across the cell membrane.	3.41	0.80	24
2.3 The rate of release of a chemical messenger from a cell is determined by the “sum” of the stimuli promoting and inhibiting that release.	3.08	0.88	24
2.4 Chemical signaling molecules can have biological effects even at low extracellular concentrations.	3.65	1.03	23
2.5 Chemical messengers that are stored prior to release can be secreted from the cell via exocytosis, or through the release of vesicles such as exosomes.	3.32	0.72	22
2.6 Cells that release messengers can be anywhere in the body.	4.18	0.85	22
3. The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.	3.46	0.98	24
3.1 The solubility of the molecule can influence how it is transported to its target cells.	3.42	0.97	24
3.1.1 Hydrophobic chemical messengers must travel with other carrier molecules i.e. binding proteins or plasma proteins	3.33	0.96	24
3.1.2 Hydrophilic chemical messengers can travel dissolved in aqueous solution, attached to a binding protein, or transported within an exosome.	3.42	0.93	24
3.2 Only the messenger in solution and free to diffuse is biologically active.	3.42	0.97	24
3.2.1 A chemical messenger bound to a binding protein in solution is biologically unavailable.	3.42	0.88	24

3.3 The extracellular fluid concentration of a messenger molecule depends on the balance between the production, release and elimination of messenger molecules.	3.33	0.96	24
4. The messenger must bind to a receptor protein in or on its target cell to produce a response.	3.78	1.04	23
4.1 Each messenger molecule binds with a certain affinity to a specific receptor molecule.	3.09	0.79	23
4.1.1 Binding of a messenger to its receptor is a probabilistic event.	2.74	1.01	23
4.2 A cell can only respond to a messenger for which it has receptors.	4.13	0.92	23
4.3 The solubility/hydrophobicity of the messenger can influence the location of its receptor protein in/on the target cell.	3.61	0.89	23
4.3.1 Water-soluble (hydrophilic) primary messengers cannot pass through the cell membrane.	3.82	0.91	22
4.3.2 Water-soluble (hydrophilic) primary messengers signal through receptors on the target cell membrane (extracellular receptors).	3.77	0.92	22
4.3.3 Lipid soluble (hydrophobic) messengers can pass through the cell membrane.	3.82	0.85	22
4.3.4 Lipid soluble (hydrophobic) messengers can signal through either intracellular (cytoplasmic or nuclear) or extracellular receptors.	3.64	0.79	22
4.3.5 Lipid soluble messengers that bind with intracellular receptors can interact with DNA to mediate genomic effects.	3.18	0.91	22
4.3.6 Lipid soluble messengers that bind with extracellular receptors can mediate non-genomic effects.	3.18	0.80	22
4.4 The number of receptors for a particular messenger is variable.	3.74	1.05	23
4.5 There can be more than one type of receptor for the same messenger on different target cells, including different isoforms of the same receptor.	3.09	0.85	23
4.6 It is the receptor that determines the cellular response.	3.27	1.12	22
4.6.1 The same chemical signaling molecule can elicit a range of cellular responses based on the receptor subtypes it binds.	2.96	0.98	23
4.6.2 Cells have a large variety of different receptors, thus enabling them to respond to a large number of different messengers.	3.48	1.16	23

5. Binding of the messenger molecule to its receptor gives rise to signal transduction.	3.33	0.96	24
5.1 A single messenger molecule bound to its receptor can lead to the activation of signaling cascades to amplify the signal.	3.04	1.00	24
5.1.1 Because the target cell response is a multistep process and amplification occurs at each step, a single molecule can activate or alter many more molecules; the more steps in the intracellular signaling process, the greater the amplification can be.	3.00	1.00	23
5.1.2 Because the target cell response is a multistep process, there are many points at which different inputs (other messengers) can modify the response. This is referred to as integration.	2.70	0.82	23
5.2 There are a number of basic mechanisms for signal transduction.	3.23*	0.97	22
5.2.1 Binding of a messenger molecule to an extracellular receptor can lead to signaling through a range of processes including the activation of enzymes, G proteins or opening of ion channels.	2.88	0.90	24
5.2.2 Ion flux can activate signal transduction pathways and alter excitability	2.91*	0.87	22
5.2.3 Binding of a messenger molecule to a receptor can regulate gene expression.	3.00	0.74	23
5.2.4 The speed of the response to signaling pathways varies according to the signaling pathway.	3.59	0.85	22
5.2.4.1 Ion channels are the fastest response mechanism	3.74	1.05	23
5.2.4.2 The signaling response for extracellular receptors and second messenger systems are rapid as second messenger molecules are already present in the cell and can be rapidly inactivated.	3.00	0.82	22
5.2.4.3 The genomic signaling effects are slower, as transcription and translation of new molecules is required.	3.26	0.96	23
6. Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.	3.04	0.86	24
6.1 Messenger release must be ceased.	4.05	0.92	21

6.2 The messenger signal can be terminated when the molecule is removed, either through diffusion (concentration becomes too low) or via chemical breakdown by enzymes or via specific transport or uptake into compartments away from the receptor.	3.22	0.85	23
6.3 The messenger molecule must dissociate from the receptor or the receptor- messenger complex, can be internalized by endocytosis and digested in the cell and the complex will cease to generate a signal.	2.96	0.95	22
6.4 Receptors can be made unavailable through internalisation, down regulation or through pharmacological antagonism.	2.87*	0.87	23
7. Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.	3.48	0.98	21
7.1 When electrically excited, current (ions) can flow from the excited cell to neighbouring cells via the gap junctions.	3.33	0.97	21
7.2 These currents then electrically excite the second cell synchronising depolarisation across the whole tissue.	3.14	0.85	21

Level of difficulty for students (1=Very Difficult, 2=Difficult, 3=Moderately Difficult, 4=Slightly Difficult and 5=Not Difficult) was rated by Task force members. SD = standard deviation. n = number of respondents. * Theme or sub-theme statistically significantly more difficult than 4.2 *A cell can only respond to a messenger for which it has receptors*. ($P < 0.05$ Kruskal-Wallis test with Dunn's multiple comparison test).

TABLE 3: Comparison of major themes for the *Cell-Cell Communication* core concepts between Michael *et al* (1,2) and this current study.

Core Concept Descriptors (CC: Michaels) or Theme (Chopin)	Michael et al 2017	Chopin et al 2023
CC1 Theme 1	A cell synthesizes and releases a chemical messenger.	Cell to cell communication occurs through electrochemical and chemical signaling and can be local or long distance.
CC2 Theme 2	Transport of messenger molecules is determined by the chemical nature of the messenger.	A cell synthesises and releases a chemical messenger.
CC3 Theme 3	The messenger must bind to a receptor protein in or on its target cell to produce a response.	The (solubility) hydrophilic/hydrophobic nature of the messenger can determine how the messenger molecule is transported.
CC4 Theme 4	Binding of the messenger molecule to its receptor gives rise to signal transduction.	The messenger must bind to a receptor protein in or on its target cell to produce a response.
CC5 Theme 5	Binding of the messenger molecule to its receptor alters cell function.	Binding of the messenger molecule to its receptor gives rise to signal transduction.
CC6 Theme 6	Termination of a messenger signal is accomplished in several ways.	Messenger signal termination requires a combination of processes that effectively prevents the signaling molecule from binding to the receptor. This can include removal of the signaling molecule from the extracellular space or rendering the receptor unavailable.
CC7 Theme 7	Some cells can communicate with neighboring cells electrically; they are electrically coupled.	Some cells can communicate with neighbouring cells electrically; they are electrically coupled via gap junctions.

Comparison of the CC themes between the Michael et al (1,2) and the outcomes of this study. Boxes with same shading (black or grey, with black or white text) indicated CC themes are common between Michael and Chopin. Unshaded boxes (white fill) indicate CC themes that are specific to the particular study. Four of the seven CC themes in each study are the same or similar, while three from each study are unaligned.