# Pancreatic Islets and Gestalt Principles

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**The human brain has inherent methodology to efficiently interpret complex environmental stimuli into understanding. This visual perception is governed by the law of simplicity, which is fundamental to Gestalt theory. First introduced in a seminal article by Wertheimer in 1923, the theory explains how the mind groups similar images and fills in gaps in order to perceive an amenable version of reality. The world we see consists of complex visual scenes, but rarely is the entire picture visible to us. Since it is inefficient for all visual data to be analyzed at once, certain patterns are given higher importance and made to stand out from the rest of the field in our brain. Here we propose that Gestalt theory may explain why rodent islet architecture has historically been seen as having a core-mantle arrangement. By filling in apparent gaps in the non–β-cell lining, the mind interprets it as a "whole" mantle, which may have further led to widely accepted notions regarding islet microcirculation, intra-islet signaling, and islet development. They are largely based on the prevailing stereotypic islet architecture in which an enclosed structure is presumed. Three-dimensional analysis provides more integrated views of islet and pancreatic microcirculation.**



Gestalt theory and its principles have been studied since the early 1920s. First described by Max Wertheimer in 1923 (1) and later explored by Kurt Koffka and Wolfgang Köhler, the origins of the theory arise from the Berlin School of Experimental Psychology. Gestalt principles were founded on the premise that humans tend to simplify their perception of the world. The results of studies examining islet architecture may have been impacted by the brain's perceptual nature and propensity for simplifying complex environmental stimuli. Humans tend to perceive an object in its entirety even when only observing a partial view of the object in question. In practice, this is a part of what constructs human pattern recognition and object permanence. For instance, the commonly used figure of Rubin's vase illustrates a situation in which a pair of faces and a vase can be viewed interchangeably, with one swapping to the "ground" of the image for the duration that the other is visible as a "figure." This "figure-ground" Gestalt principle demonstrates the mutability of perception. In this manner, the human brain is able to simplify the chaotic world around it and create structure from the somewhat disconnected and separate pieces of information that the senses perceive. Gestalt theory also describes many natural perceptive shortcuts that the human brain likely employs in order to simplify incoming information, as well as shortcomings stemming from those approaches. We found that previous methods of studying the pancreatic islet may have been influenced by several of these Gestalt principles, including the following: figure-ground articulation, similarity principle, continuity principle, closure principle, the law of common fate, and the laws of Prägnanz/simplicity. In our further discussion, we will describe how commonly accepted notions of islet architecture and microenvironment may have been influenced by Gestalt principles. In addition, we will describe how observation in three dimensions (3D) may help future studies to overcome this Gestalt disposition.

In this Perspective, we examine where the prevailing notions of rodent and human islet architecture first originated, such as the existence of a mantle-core structure and islets having a pattern of blood flow distinct from their exocrine surroundings. Since they have been almost exclusively studied in two dimensions (2D), we hypothesize that past imaging techniques might have impacted the perception and, thus, the interpretation of experimental results. Further examination of human perception demonstrates how human nature may play a critical role in the conjectures that arise in islet studies.

## Mantle-Core Arrangement of the Rodent Islet: Continuity and Closure Principles

As early as 1907, it was recognized that β- and α-cells had a specific arrangement in the pancreatic islets of rodents

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(2). It has since become consensus in the field that the mouse islet contains a core of β-cells surrounded by a continuous mantle consisting of α- and δ-cells (3–8). This arrangement has been widely accepted for decades and has influenced our understanding of pancreas function.

Biases in human perception may have played a role in the development of a dogmatic perception of a mantle-core structure in the rodent islet. In Gestalt theory, many of such cognitions are outlined in what is known as the principles of grouping (9). Among these principles, the concepts of continuity and closure are closely related. The principle of continuity observes that when separate units are in alignment, they tend to be seen as a unified whole. Such a whole can then be further perceived as one single closed object in accordance with the principle of closure (in which the "ring" shape is viewed as simply being obscured rather than broken) (Fig. 1*A*). In a 2D view of an islet, it may appear that α-cells in the periphery form a mantle following these two principles (Fig. 1*B*). Previous studies of islet architecture in rodents have examined thin sections of pancreas, which required researchers to study 3D islet architecture in 2D. Although mouse islets may contain a somewhat incomplete mantle when viewed in 2D, this "mantle" formation is lost in its entirety when the islet is viewed in 3D (Fig. 1*C*) (10). Studies that have used 2D images of islet architecture have been limited in that they capture only a single-plane view of islets that may show extensive architectural changes in the 3D view of the same islet. This may be attributed to the poor resolution in the *z*-plane of commonly used microscopes in these studies. Additionally, the formation of a complete mantle is mathematically possible only for islets of exceedingly large size (>400 μm effective diameter [11]). A complete mantle consisting of a single-cell-thick exterior layer of non–β-cells would require a whole-islet proportion of non–β-cells larger than what has been previously observed in islets of this size. Islets of more commonly observed size ranges would require a significant proportion of their endocrine cell population to consist of non–β-cells. For example, an islet with β-cell core diameter of 100 μm and a complete non–β-cell mantle would consist of 54% non–β-cells, with the proportion greater than 20% in islets with a β-cell core diameter up to 400 μm. It is acknowledged here that α-cells constitute the majority of non–β-cells in mice and thus historically have been regarded to represent "non–β-cells" (12). However, pancreatic endocrine cells include other cell types such as δ-, pancreatic polypeptide, and ε-cells (13). Relatively low abundance of these cells is unlikely to reveal an islet mantle, even when they are included.

### The Prototypic Human Islet: Similarity Principle

While the principles of continuity and closure provide a partial picture of why pancreatic islets appear enclosed, other Gestalt principles can elucidate similar biases within the scientific community. For instance, the similarity principle describes the mental grouping of elements that share similar characteristics such as shape, size, and color (Fig. 2*A*). Islets may be perceived as identical if they share one or more similar traits (such as size, shape, or cellular distribution). For example, one may expect two large islets to have a similar endocrine cell distribution when they most likely have very different internal compositions (14). Even external factors unrelated to the appearance of the islets themselves might lead to preconceptions about islet number and cell composition, such as similar BMI, sex, age, and even the weight of the pancreas itself (15). For example, correlations of these parameters with β-cell/islet mass are relatively low despite statistical significance ($r^2 < 0.3$). Thus, the similarity principle of Gestalt may extend to previous studies where these external factors were considered predictors of postpurification islet yields.

The islet cytoarchitecture found in commonly used laboratory mice is more or less similar where β-cells form a core surrounded by a scattered shell of non–β-cells. Therefore, it has generally been considered to have "prototypic islet architecture" for a long time (Fig. 2*B*a). Here, it is important to recognize "islet plasticity" in terms of cytoarchitecture across species (16). In horses and cats, for example, the core of islets is formed by α-cells rather than the expected β-cells, with β-cells themselves being clustered in the periphery (17–22). Even within mice, α-cells have been observed in the central core of islets under conditions of increased demand for insulin such as inflammation (prediabetic nonobese diabetic mice), pregnancy, and insulin resistance (*db/db* mice) (10) as well as in several transgenic mouse models (23–26).

With this decades-long view of rodent islet architecture in mind, human islets were found to be strikingly different. They were described as having β-, α-, and δ-cells "randomly dispersed or scattered throughout the islets" (27,28). Since then, this state of intermingled endocrine cells has somewhat become "the prototypic human islet" (Fig. 2*B*b). In theory, this architecture would conveniently allow investigators to examine a relatively small number of islets per subject. Indeed, while humans can have 1 million islets in their pancreas (29), many studies have sampled only a few islets in an attempt to replicate the human environment ex vivo. Further, some single-cell studies only examine ~50–80 cells per donor. In the context of these approaches, we recently examined the heterogeneity of the human pancreatic islet to understand the potential limitations of studies that use a small sample size of islets (14). We found that the endocrine cell composition of islets varied not only between subjects but also among islets from the same individual (Fig. 2*C*a). As a conceptual test of previous studies that aimed to characterize human islet cell composition, we determined that a minimum number of 400 islets would need to be studied from an individual donor in order to build a 95% CI of width 5% around the proportion of β-cells within the islets of that individual (14). Simply, sampling more islets from an individual allows for greater precision or certainty when attempting to characterize islets by endocrine cell composition. While

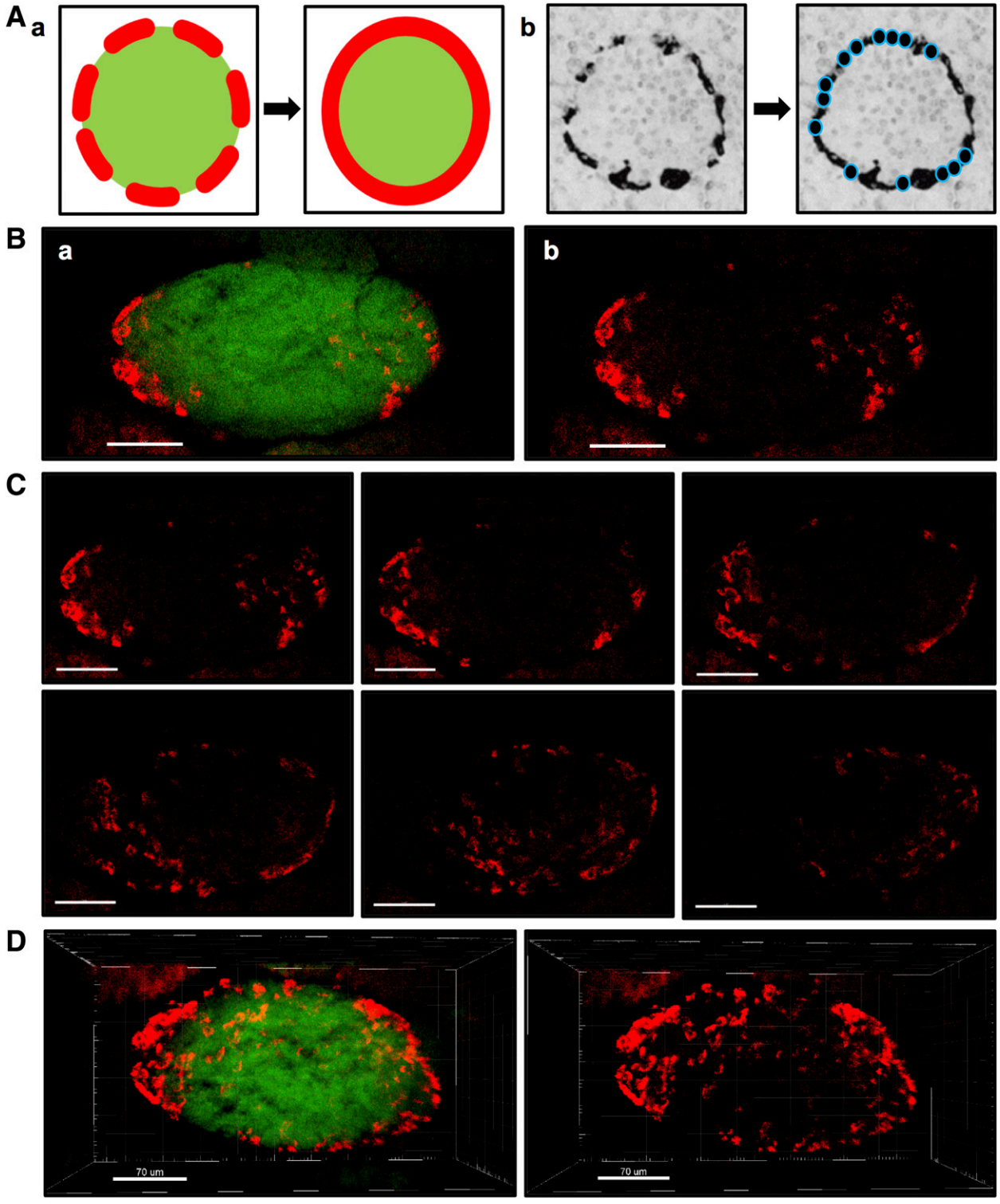


**Figure 1—** Mouse islet architecture and the Gestalt principle of closure. *A*: (a) Simplified illustration demonstrating the principle of closure. The interspersed non–β-cells occupying the outer mantle might have been inferred to be continuous rather than incomplete, thus propagating the common notion of a non–β-cell mantle in mouse islets. (b) The principle of closure applied to a 2D histological section of islet non–β-cells. On the left, a 2D section of a mouse islet stained for glucagon shows α-cells occupying the islet exterior, with gaps in the outermost layer. On the right, an artificial expansion of the incomplete mantle that would be necessary to comprise a complete mantle, perhaps a result of the Gestalt principles of continuity and closure. *B*: (a) Single-plane confocal image of a mouse islet immunostained for insulin (green) and glucagon (red). (b) α-Cells only. *C*: Cross sections of glucagon signal taken in 20-μm increments. Of important note is the change in α-cell distribution with changes in *z*-depth. α-Cells occupy different areas of the islet exterior at different *z*-depths. Depending on the level at which the slice is taken, the islet exterior may appear nearly incomplete or more complete with α-cells. However, at all levels, no complete mantle formation is observed. *D*: 3D reconstruction. Scale bars: all 70 μm in *B*–*D*.

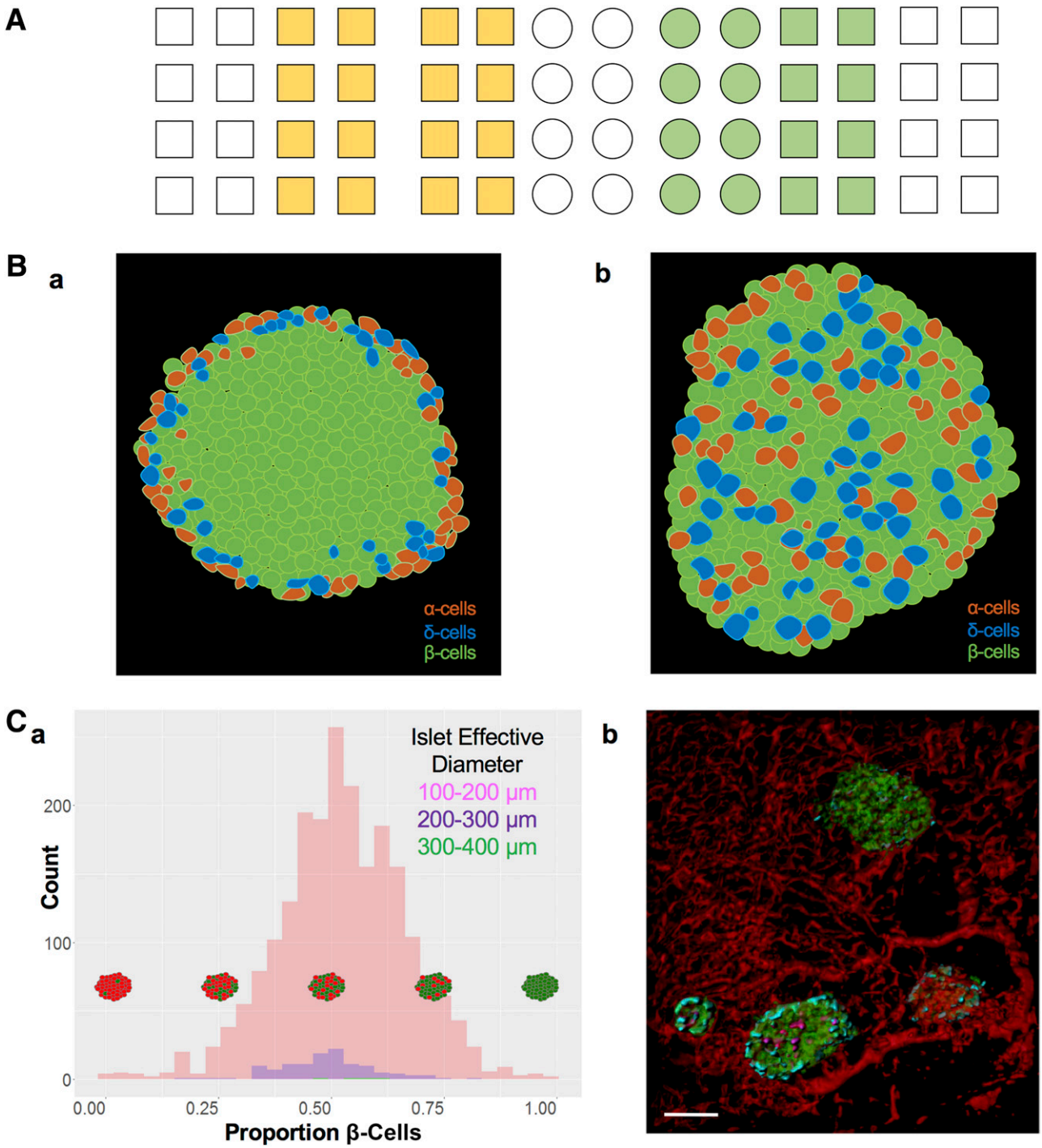


**Figure 2—** Prototypic human islets: similarity. *A*: A simplified illustration of the principle of similarity. Despite the identical shape of the squares on the left side of the image, the mind tends to group those colored yellow in one group and the white ones separately. Further, it seems natural to group the green circles and green squares together, although the green circles are immediately adjacent to white circles on the left, and the green squares are immediately adjacent to white squares on the right. *B*: (a) Prototypic mouse islet: insulin (green), somatostatin (blue), glucagon (orange). The prototypic mouse islet has been described as uniformly containing a core of β-cells and exterior of non–β-cells. Mouse islets have been considered to contain similar distributions of endocrine cell proportions. (b) Prototypic human islet. The prototypic human islet has been described as having an interspersed architecture, with β-cells and non–β-cells intermingled throughout. *C*: (a) Distribution of β-cell composition sorted into three diameter ranges from a whole pancreas analysis ($n$ = 10,964 islets; 43 year old male) (10). Although the proportion of β-cells within these islets was nearly normally distributed, there exists marked heterogeneity of islets within the same individual. This includes islets consisting almost entirely of β-cells and separate islets consisting almost entirely of non–β-cells. Despite having one- or multiple-characteristic similarity (size, donor, etc.), these islets display clear distinguishing features (endocrine cell distribution) when examined on an individual level, separate from others that may appear "similar." (b) 3D rendering of human islets: insulin (green), glucagon (cyan), somatostatin (magenta), and CD31 (red). Similarly, although these selected islets exist in the same region, they vary noticeably in size and endocrine cell composition. Scale bar: 100 µm.

this number may appear large at first, we found that sampling too few islets, such as 5 or 10 as has been granted in the field, would provide widely variable measurements of islet cell composition in any given individual. It is also important to note that the number of islets necessary to achieve this level of certainty will vary depending on the parameter of interest. Furthermore, by conducting 3D analysis of islet architecture using fluorescence confocal microscopy, it was determined that the concept of a prototypical human islet is not consistently observed in pancreatic tissue slices. For example, a selected group of islets from the same region of pancreas may differ markedly in size, shape, and endocrine cell architecture and composition. Similarity in one aspect (location) does not confer similarity in other characteristics (Fig. 2*C*b).

### Subunit Formation in Human Islets: Continuity, Closure, and Law of Simplicity

Related to the perceived "mantle-core" formation in rodent islets described above, a similar concept surrounding the formation of "subunits" has been proposed in human islets (4,30,31). Again based on 2D imaging, human islets were considered to be composed of several mantle-core subunits. However, many of the images used to come to this conclusion depict an incomplete lining of α-cells. This partial enclosure could easily have been perceived as a mantle as described by Gestalt continuity and closure principles (Fig. 3*A*). Effectively, the "dotted line" of α-cells surrounding the core of β-cells is seen as a contiguous surface, a full "ring," or else, extrapolated to 3D, as a "shell" that encapsulates the β-cell core. This is compounded by the law of simplicity, a fundamental principle of Gestalt theory that describes how humans perceive the world in terms of their experiences or what is "most likely" (similar to the principle of Occam's razor that the easiest explanation tends to be the right one). In practice, this allows humans to take less time and effort to mentally organize a familiar environment. The mind suggests that a mantle indeed must be present based on prior experience with the everyday world. However, microscopic images can be deceiving. One simple example of these principles in action can be found in the Olympic rings, where we can mentally separate the logo into five distinct contiguous ring "subunits" and not see it as a single, odd-looking shape. In 2D, it may appear that α-cells form subunits similar to the mantle-core structure in mouse islets (Fig. 3*B*). However, 3D analysis of a whole islet does not show subunits with such an arrangement (Fig. 3*C*).

### The Islet as an Enclosed Independent Micro-organ: Figure-Ground Articulation

The islet has long been considered an independent micro-organ "embedded" in the exocrine pancreas. In support of this, islets can be enzymatically isolated from the pancreas and respond to glucose and other secretagogues in vitro. In fact, the islet is often illustrated as being situated between an afferent arteriole and an efferent venule, indicating one-way traffic of islet blood flow from artery to vein with no integration to the surrounding exocrine capillary network (32–34).

However, this lack of integration with exocrine tissue may very well be another artifact of human perceptive capabilities. In Gestalt theory, the concept of figure-ground perception refers to the visual system employed by the mind to separate the visual field into two distinct components: the main object (the figure) and the background (ground) (Fig. 4*A*). Due to the differences in cell type and architecture, the islet may have been perceived as a separate object when compared with the rest of the pancreas (i.e., exocrine pancreas). While islets are indeed different from their surrounding tissue in terms of composition, their constituents may very well be fully integrated with the rest of the pancreas itself via an integrated microcirculatory pattern (Fig. 4*B* and *C*).

### Isolated Islet Blood Flow: Common Fate

Finally, closely related to all four preconceptions described above, islet blood flow has naturally been considered to be isolated from the microenvironment in the pancreas across a wide variety of species (32). Here, we hypothesized that blood flow in an enclosed islet may be perceived as a single "stream" having "common fate," another Gestalt principle of grouping in which visual objects perceived to have similar directionality are seen as part of a single whole (Fig. 5*A*). In essence, if the human mind perceives either objects with similar directionality or objects moving as if they were part of a whole, it tends to see them as a single object. For instance, a marching band can form recognizable shapes as seen by the crowd above.

Foundational studies have attempted to characterize the microenvironments of rodent and human pancreatic islets since the 1950s (35). Since then, seminal work by Orci and colleagues has focused on the cells that comprise the islet to further understand their role in the pathogenesis of diabetes (4,32,36,37). In 1995, the field had a legendary meeting strictly focused on the debate over three models of the islet microcirculation, which were built upon research of an impressive number of articles (>70) published between 1969 and 1995 (12). These three models were starkly different from each other, and each model implied an ordered secretion of endocrine hormones into the local vasculature. Notably, each model proposed relied heavily on the accepted dogma of rodent islets consisting of a non–β-cell "mantle" surrounding a core of β-cells (Fig. 5*B*). In brief, model 1 proposed that blood first perfused the non–β-cell periphery before entering the islet core. Model 2 described the opposite, with blood flowing into the β-cell core before perfusing the non–β-cell mantle. Model 3, on the other hand, simply suggested that blood flowed from one side of the islet to the other irrespective of islet cell type. Model 3 also described gated channels that could modulate blood flow to and within islets. It is noteworthy that the meeting participants overall agreed that all three types of blood circulation could occur based

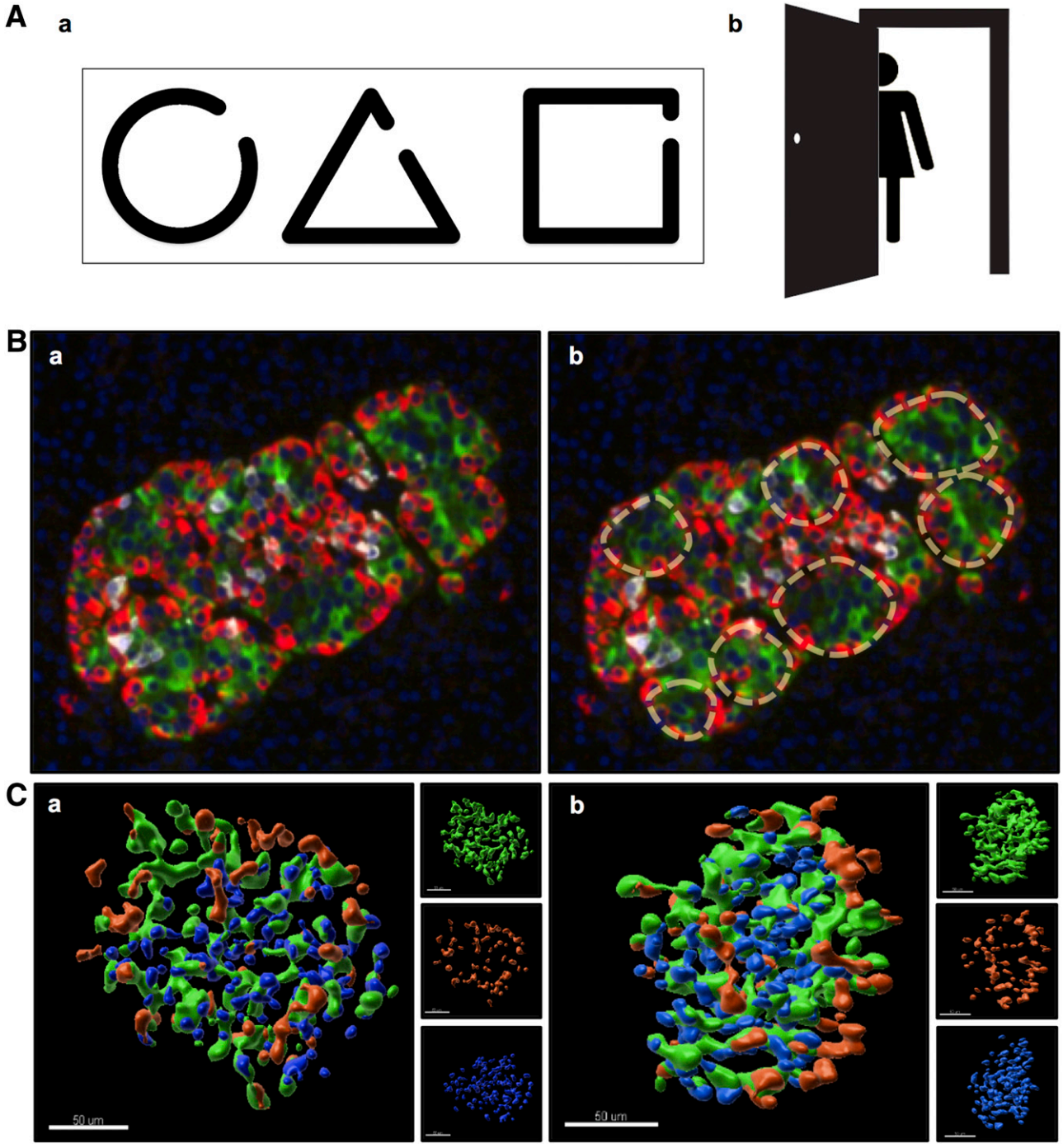


**Figure 3**—Human islet architecture and the Gestalt principles of continuity and closure. *A*: (a) A simplified illustration demonstrating the principle of closure using three basic shapes. The mind tends to automatically complete the closure of these incomplete shapes, and they can be easily recognized as a circle, triangle, and square. (b) The principle of continuity helps us recognize a person when only a partial figure is present. When only part of a unique object is readily available for observation, the mind tends to "continue" its existence in order to accurately identify the unknown object. *B*: (a) 2D image of a human islet immunostained for insulin (green), glucagon (red), somatostatin (gray), and DAPI (blue). (b) Dashed lines highlighting regions perceived as individual "subunits" due to the non–β-cell arrangement. Although these individual "subunits" are incomplete in the 2D view, the principles of continuity and closure make it easier to group each area as its own contained subunit. This occurs despite the intermittent breaks in the subunit "mantle" of non–β-cells and "core" of β-cells. *C*: (a) 3D rendered view of a human islet. Insulin (green), glucagon (orange), and somatostatin (blue). Views of individual channels are shown on the right. (b) Side view of *C*a. In 3D, the whole-islet distribution of endocrine cells can be appreciated, especially with regard to the localization of individual types of endocrine cells. Visualization in 3D essentially captures all possible 2D slices that may exist within the islet, allowing the observer to better appreciate the true lack of continuity of "subunit" formation. Scale bars: all 50 μm.

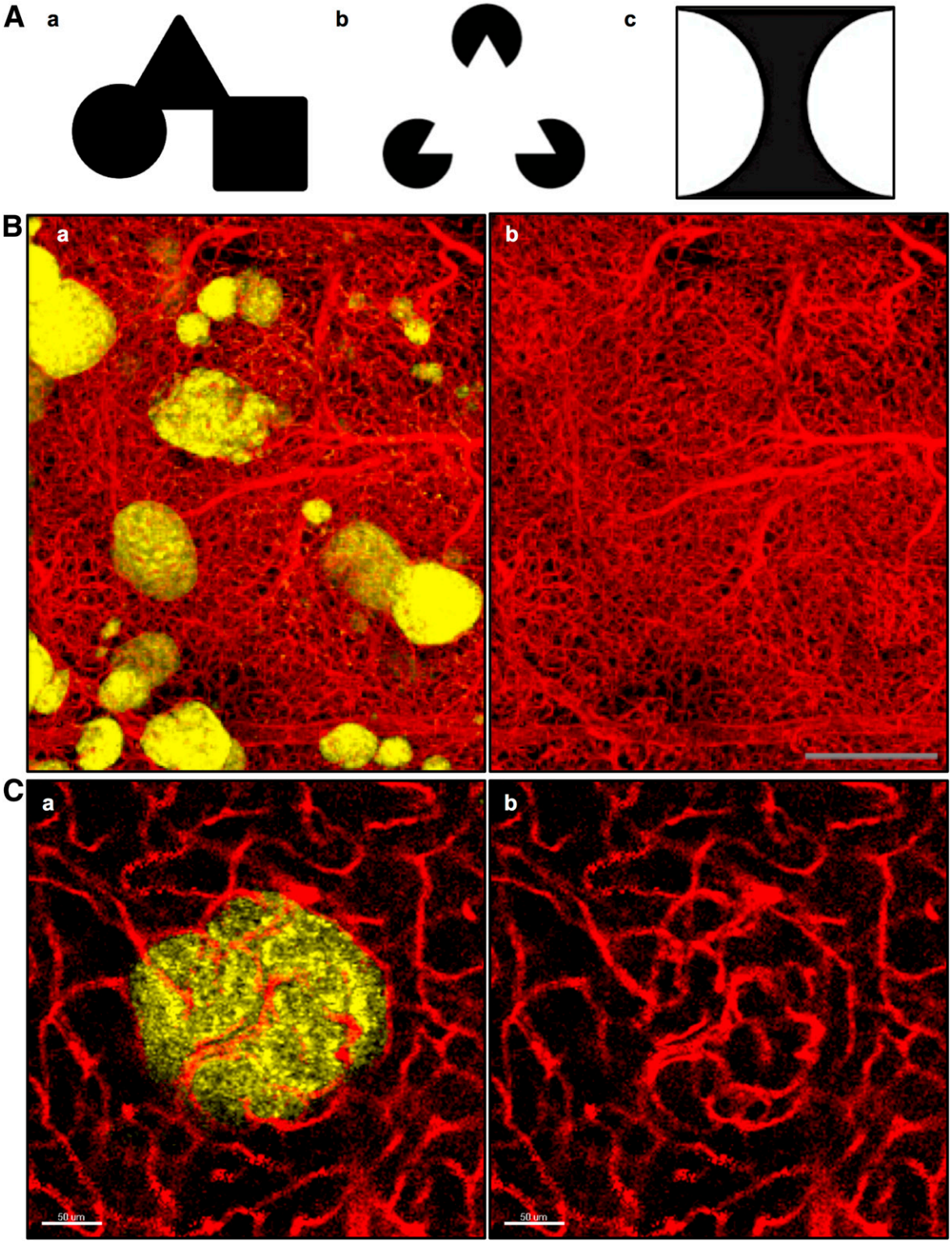


**Figure 4—**Islet as an independent micro-organ: figure-ground articulation. *A*: Three simplified illustrations that demonstrate figure-ground articulation. (a) Although the black figure technically encompasses a single polymorphic shape, the mind tends to separate the image into three individual and familiar shapes. The space (ground) between the distinct shapes (figure) allows for the recognition of these three entities. (b) A triangle is quickly perceived although one is not explicitly drawn. Instead, three incomplete shaded circles (figure) create a new triangle image out of empty space (ground). (c) A single hourglass shape (figure) creates two circles (ground) with its edges. *B*: (a) 3D image of human islets (a pan-endocrine cell marker, HPi1, in yellow) and vasculature (CD31 in red). (b) Vasculature only. Distinct islets (figure) may appear as separate entities from the surrounding vasculature (ground). When viewed alone, the vasculature gives little indication as to where islets might be localized. Instead, islets are simply integrated into a larger, continuous pancreatic vascular network. Scale bar: 50 µm. *C*: (a) An enlarged image of a single human islet and the surrounding capillary network. (b) Capillaries only. Local islet capillaries appear continuous with the nonislet vascular network, and intra-islet capillaries take on no distinct shape or pattern when compared with extra-islet capillaries. Scale bars: 50 µm.

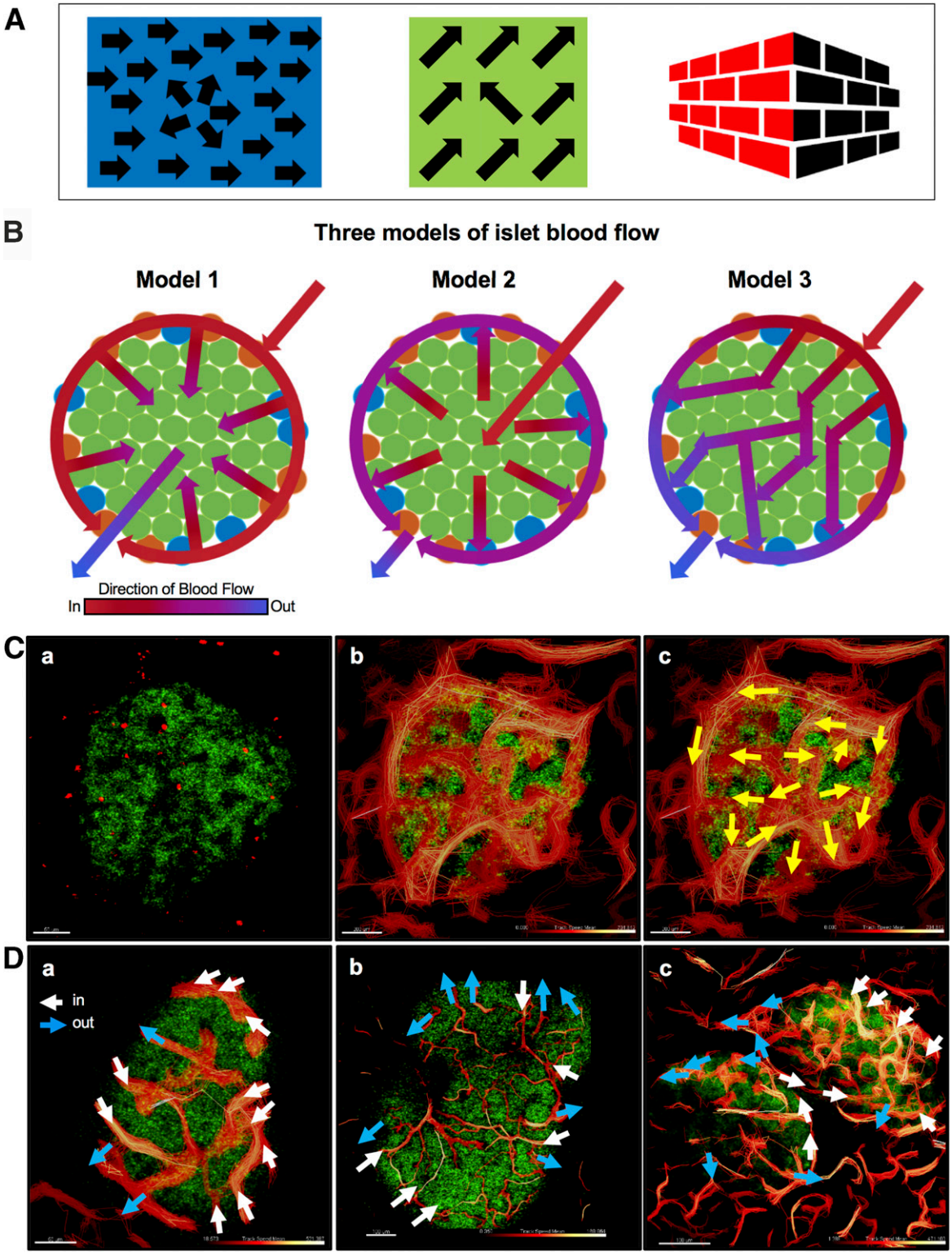


**Figure 5—**Blood flow within the islet: common fate. *A*: Three simplified illustrations that demonstrate the principle of common fate. (a) A group of arrows may be perceived as all generally pointing in the same direction, although some point elsewhere. (b) Similarly, almost all arrows of a group travel in the same direction (similar to ducks in a flying "V"). (c) Similarly colored shapes appear to follow a common pattern of directionality (red from center to left, black from center to right). *B*: Three previously proposed models to describe islet blood flow, where all entering blood cells were perceived to travel in the same direction. Model 1 shows an external-internal direction of flow, model 2 shows an opposite internal-external flow pattern, and model 3 describes a side-to-side polar pattern. *C*: (a) Intravital fluorescent image of β-cells (green) and red blood cells (RBCs) (red) in a mouse pancreas. (b) Fluorescent image of β-cells and heat map showing mean RBC speed in the islet microcirculation. Slow (red) to fast (white). (c) Arrows indicating the direction of RBC movement within the islet at a confocal plane. Scale bars: all 50 μm. *D*: (a–c) Arrows displaying the direction of RBC blood flow along the endocrine-exocrine interface. From exocrine (islet) to endocrine: in = white arrows. From endocrine to exocrine: out = blue arrows. Although blood cells may approach the islet from one or a few

on both morphological and intravital evidence (12). Over a decade later, Nyman et al. confirmed the existence of all three patterns of blood flow with model 2 being the most prevalent (38).

We recently revisited this unresolved debate of islet blood flow, using a system that allowed us to track individual red blood cells as they perfused the islets of mouse insulin I promoter (MIP)-GFP mice (11,39). It should be noted that we are continuing our study of islet blood flow in mice and humans using 3D imaging techniques in an effort to further characterize our current model of islet blood flow, which is based on a previous study of 391 islets in 192 mice (11). Previous methods used to study islet blood flow in mice, such as a bolus ink or dextran injection and corrosion casting, might have been limited in their ability to track the direction and speed of blood flow within islets. We also used a 3D imaging technique using thick pancreatic tissue slices from human donors to visualize the vascular structure within both the endocrine and exocrine pancreas (11,40). Our 3D imaging of human pancreatic tissues revealed that human islets were integrated into an extensive capillary network within the pancreas. Previous studies appear to have regarded islets as an independent and unintegrated micro-organ, with a capillary network uniquely isolated to the islet. However, we show that the islet vascular network is entirely integrated with blood vessels in the endocrine tissue (11). Similarly, in in vitro experiments, the islet is assumed to be an "enclosed" functional unit. Isolated islets lose a substantial amount of endothelial cells through the isolation process and in culture (41–43). Caution needs to be taken when interpreting in vitro experimental results, since isolated islets can behave differently (44).

## Discussion

Gestalt principles depict the capability of the human brain to fill in missing information and generate whole forms from lines, shapes, and curves. It may not be well appreciated, but several Gestalt principles are ubiquitous in our daily lives, often seen when used by advertisers as a strategy to promote their businesses. Space and contrast can be used to create a stable figure-ground relationship with a clear distinction to attract attention and send an important message to customers. The law of closure is often applied to simplify icon designs by providing only sufficient information so that the human brain will complete a shape or object. One well-known logo that employs this is that of FedEx with a hidden arrow. The clever use of the negative space between the last two letters elegantly and playfully conveys the company's message of reliable and speedy delivery services.

In medicine, Gestalt principles yield significant implications in many clinical and research areas. Particularly in radiology, visual perception is critical for accurate diagnosis. Koontz and Gunderman (45) described the value of understanding the benefits and risks associated with Gestalt principles focusing on radiology education. The authors further pointed out a holistic approach of Gestalt principles as they are applicable to general clinical practice. Gestalt principles were born with holistic approaches challenging the theory of atomism that was the predominant psychologic theory at the time (46). Atomists suggested that perception could be broken down into discrete units and thus it would be constructed in a "bottom-up" fashion from such elements, whereas Gestalt psychologists held that perceptions would be perceived globally, in a more "top-down" fashion. For example, in a clinic, a physician practically needs to have a global impression of a patient's health status within seconds of entering the room (45). As an example, the holistic approach of Gestalt principles is practiced by radiologists with two distinct processes when interpreting a radiograph: a rapid global search followed by a secondary systematic scan (45).

In this sense, we propose to start to see the islet as a whole together with its surrounding microenvironment, then try to dissect details in a top-down fashion. This approach could result in challenging some of the previously established concepts as described above. Previous assumptions regarding islet architecture, endocrine cell composition, and intra-islet blood flow are in fact all related stemming from the very first assumption that the islet is an enclosed structure, where blood perfusion has been considered to be regulated independently from that of the exocrine pancreas. It may be because of these assumptions that the endocrine and exocrine pancreas have historically been studied separately by different fields of investigators, and pancreatic diseases are treated by physicians in different medical disciplines. However, imaging thick pancreatic tissues recently revealed that blood flow between endocrine (i.e., islets) and exocrine pancreas persists in a manner that physically links these two parts of the pancreas as a single organ through the integrated pancreatic vascular network (11). The limitations of previously used imaging techniques, especially static 2D imaging, along with the intellectual influence of Gestalt principles, may have led to this contrast among investigators.

As the accuracy of clinical Gestalt (i.e., the overall clinical impression) used for diagnosis has been intensely debated to date (47–49), it is worth repeating that understanding the benefits as well as risks associated with Gestalt principles is crucial. Gestalt principles are an important part of many forms of research and medicine as

feeding arterioles, the directionality of individual blood cells does not follow a specific pattern that aligns with the principle of common fate. Some vessels may bring blood cells from interior to exterior, and immediately adjacent vessels may move blood cells in the opposite direction. Furthermore, patterns of flow vary markedly across individual islets. Scale bars: 50 μm (a) and 100 μm (b and c).

a whole. Being aware of these principles allows for a greater degree of vigilance when it comes to making reasonable assumptions about incomplete data. While the human mind is excellent at creating order from chaos, it does not always provide us with accurate information, especially in unfamiliar environments.

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